

Usher Syndrome Coalition | The Role of RNA Therapies in Usher Syndrome

Ladies and gentlemen, thank you very much for the invitation. It's a great honor to be allowed to present our latest clinical data. My name is Friedrich Asmus. I'm Vice President of Clinical Development at ProQR Therapeutics. ProQR Therapeutics is a globally acting biotech company with our headquarters in Europe in Leiden.

Next slide show, our forward looking statements. So what is ProQR? ProQR has a clear mission. ProQR is a patient-centric RNA therapeutic platform, developing drugs for orphan diseases with well understood genetic causality. So it is about developing meaningful drugs. It is capitalizing on a uniform platform, which I will talk about and explain to you what RNA therapeutics are. And all of our programs are executed in rare and ultra-rare diseases where there is only a limited number of companies really developing therapies. So the unmet need is, here, extensive.

ProQR has already reached the clinical stage, which means that we have clinical studies ongoing, not only developing drugs before the use in men. And there are three programs that are currently active. The one and the front runner of the program, the drug is called seprofarsen. It is for Leber congenital amaurosis type 10, which is the most severe form of congenital genetic blindness. This program is in an advanced stage, in the registration trial phase.

And then, last year we started two programs in retinitis pigmentosa slash Usher syndrome. The QR421a program, which I will expand on over the next 15 or 20 minutes, this is for patients with mutations in Exon 13. It's a specific coding sequence of the Usher gene called Ush2a. And then there is another program in early clinical development for autosomal dominant retinitis pigmentosa with a specific and highly frequent mutation in the Rhodopsin gene.

ProQR has undergone a specific journey to become a player in the development of drugs for genetic eye diseases. The company started eight years ago. The anniversary was celebrated by us on the eighth of May. It was a company initially focusing on another rare disease, which is called cystic fibrosis. But early on, the founding members of the company detected that there is a huge unmet need also in ophthalmic diseases with genetic causes.

And so, they joined forces with academia. And early on also with a patient organization to really get a handle and a jumpstart in getting a preclinical program together. There is also an extensive in-house working force working on establishing the programs. And this allowed that in more or less three to four years. The company was able to start already the first clinical program in its most severe form of

congenital genetic blindness called LCA 10.

This is a successful program that over these two to three years now has already reached the registration phase because the first trial showed very promising results. And on top of that, we have moved two further programs into a clinical development stage, which I already alluded to on the Usher study and also the rhodopsin study.

And this is not the end of the story. It's more or less the beginning because our pipeline comprises over 25 additional compounds for different mutations. So hopefully this will continue and address also an unmet need in conditions and subconditions where there are even fewer patients than in the normal or orphan disease.

The prerequisite for doing so is that ProQR has built a platform for executing all this precision medicine. So it's a shared chemical backbone, the so-called RNA oligo-nucleotides. They are more or less patching mutations, the errors in the DNA. And that is a versatile approach. And then we are building on a rather abundant and well established administration mode. It is called intravitreal delivery that is done in age-related macular degeneration or diabetic eye disease regularly. So we know about the risks. We know about how to apply procedures that guarantee and optimize safety.

And as opposed to other therapies, like gene therapies, that require more sophisticated surgical procedures from the retinal specialist, this is a drug that distributes readily to affected tissues in the eye. So it also has the opportunity to reach central and peripheral diseases because it's not confined by a certain, for example, injection or surgical technique under the retina.

And last but not least, we have specific models so-called the optic cup model. These are organoids, so artificial organs built from stem cells, that can be erased with patient stem cells that carry the mutation and offer a unique opportunity to test drugs at an early stage and to come up with first dose estimations that then could be moved in the clinic.

So some more detail on these retinal organoids. It's important-- and this is something that we are advocating a lot-- that all our patients get the opportunity to donate or to participate in a skin biopsy program. It's a small skin biopsy that can then be expanded and developed into a small eye-like structure. And this can be then used for potentially testing new drugs or even the specific drugs for patients in the lab.

And this allowed our front runner program, the LCA program, to already quite reliably estimate a dose that is clinically meaningful. So here in the middle, you see a graph. On the left hand side is the

normal control number of copies in the cells with which a specific protein can be produced untreated in a patient's situation where there is almost no copy. And by patching the error in the DNA, this copy number is largely restored. You don't need the full copy number of normal healthy subjects but have to restore it to a certain extent to see a therapeutic benefit, which we saw already in this LCA trial.

And of course, having a dose estimation is a relatively straightforward and quick way into having already, in the first clinical trials, a meaningful clinical response that you then can build on. Specifically important if the patient number is limited and the condition is ultra rare.

Let's look at the mode of action of QR421a. It has a specific molecular mode of action that it skips mutated sequences off the DNA that have a flaw. And in a transcript, this flaw is then removed. So if you look at the left hand schematic, there is a photoreceptor drawing and usherin transports important functional proteins through the photoreceptor. This is only guaranteed when the protein has the normal composition. So the normal order, Exon 12, 13, and 14 in the coding transcripts of so-called mRNA.

In case you have mutations in Exon 13, either the protein is shorter, non-functional, or the coding information from the mRNA is deleted from the cells. So there is a lack of usherin protein. And the protein trafficking in the photoreceptor cannot commence.

QR421a here has the effect that it patches the mutation in Exon 13. The transcript is then one that lacks Exon 13 but still is functional and able to provide a proper support for transport of proteins through the photoreceptor.

Building on that optic cup retinoid model, we also were able to estimate a good starting dose we know now from the interim results, which is 50 micrograms. You see here in the schematic that you already start having a response at one microgram. In that model, that equates to roughly 50 micrograms. And therefore, the study design of the so-called STELLAR study, the first-in-human study, also has the 50 microgram dose as a starting dose. And then there are additional dose levels, 100. And the highest dose level that we are currently investigating is 200 micrograms.

So what is RNA therapy? I briefly touched on it already. I touched on the individual route of administration, that this is an established route of administration that can be done by essentially every retinal specialist. The administration itself is not different from other drugs that are frequently given for other diseases. The injection, however, is likely less frequent. So two to three injections per year may be sufficient to have a continued effect. And there is no additional chemistry other than the molecule itself. So there is no viral vector. There is nothing in addition. It's just a naked molecule, an

RNA molecule that exerts the effect.

Also as this is not a complex surgical procedure, the drug is distributed through the eye to essentially all tissues and therefore affords for broad ability to target certain tissues not only in the center but also in the periphery. And you all know that, in Ushers and retinitis pigmentosa, much of the disease progression happens not in the center but also in the periphery. So broad distribution may be favorable, specifically for these diseases.

What is the key of the evolution of the symptoms that Usher and retinitis pigmentosa patients have? You all very well know that. This is just for recapitulation. It starts in childhood with night blindness. Then the visual field loss progresses. And finally, also central vision, so a reading vision, is impacted and gone. And in the worst case, patients even progress to light perception only.

How can that be measured in a clinic? So there are two ways of looking at it with certain assessment techniques. One is visual field. So how broad is the visual field? And the other is visual acuity, which is a central foveal vision. So center of the retina function. And there are also standard ways of measuring visual acuity.

For the visual field, we have in our trials currently three different modalities. Microperimetry looks more in the center. Automated perimetry looks for the breadth of the visual field. And there is a specific form looking at raw function at visual field at low light levels. That is called dark adapted chromatic perimetry. And in the schematic, you see that, in different disease stages, the visual field gets narrower and narrower. And of course, if the progression is too slow, that puts the process on hold or even--

And then there is a functional test on light sensitivity of the retina called the full field field stimulus threshold test. It's applied to all patients in this STELLAR trial. And it's capturing the performance of the most sensitive part of the retina. And this test showed a directional improvement in the treatment group. And it can be taken as an indicator of an increased light sensitivity.

In addition, we are also interested in the structure of the retina and of the photoreceptors because Usher syndrome and retinitis pigmentosa are degenerative diseases. So there is loss of retinal structure ongoing. And this can be captured with optical coherence tomography.

The degeneration of photoreceptors cells can be measured by this specific parameter called the ellipsoid zone. You see that on the right hand side in lilac. The photoreceptor layer is called the outer nuclear layer. And these measures allow a reliable delineation of the extent of photoreceptors and

their loss over time. The therapy would here slow or hold the progression of deterioration.

So what is the trial design like on the STELLAR trial, the Usher trial? The objective was to really establish early safety and tolerability and characterize early examples of functional target engagement, which means, of course, for a first trial, you don't claim to have the exact dose and the dosing interval. But you want to see if the doses and the way you administer the drug have the potential to yield meaningful improvements and have the potential to be moved to further clinical studies.

This is how the so-called STELLAR trial looks. It has four dose cohorts, as we alluded to briefly, 50, 100, and 200 micrograms. The first cohort comprised of four active early treated patients. And as a control, four patients in whom it was pretended that they received the treatment, so-called sham procedure patients. Then the dose was escalated, after the safety of the 50 microgram dose was demonstrated, to 100.

And then an interim analysis was performed to see where we stand in respect to safety and also therapeutic effects. And currently, a little bit delayed by the COVID pandemic. We are including patients in the cohort 2B and three to hopefully finish the trial in a couple of years from now with the last patients. And to have further readouts at the end of this year on the higher doses and longer follow up of the previous cohorts.

So this is the trial population as it entered the interim analysis. Four patients on 50 micrograms. Four patients on 100 micrograms. Six patients receive the sham control treatments and no active treatment. It's important to know that all of us have two copies of a gene. If you have mutations in usherin, you need to have two mutations to get the disease.

In this specific case, we looked specifically at mutations in Exon 13. So some of the patients had two mutations in Exon 13. They're called here homozygous. And for example, in the 50 microgram group, there were three patients with mutations in each of the Exon 13 alleles they had. And one heterozygous, so this patient had another mutation on another spot of the gene.

Phenotype varied. It was rather balanced. At least in the actively treated group, 50% had an Usher presentation with hearing impairment. And 50% didn't have hearing impairment. And also the visual acuity and visual function level was more or less similarly distributed with two mild to moderate in the 50 microgram group and three in one 100 microgram group.

And the follow up, of course, varied as did the trigger for the interim analysis was at least three

months. The 100 microgram group had three to four months follow up. And the 50 microgram had almost up to one year follow up.

So how do the results look? So we looked all together over 1,350 subject treatment days in the eyes. There were no serious ocular or non-ocular adverse events. There was no evidence of inflammation and no treatment-associated cataracts. So that can be one of the adverse events that are of interest if, after treatment, the lenses become opaque or blurry and need replacement. But that was not observed. There can be also toxic effects at very high doses to the retina called cystoid macular edema or retinal thinning. And also this was not observed.

This is the core slide. So on top of the beneficial safety, the favorable safety, how did the efficacy look? So 25% of treated subjects were defined or could be categorized as responders. And they were called Responder One and Responder Two. And I want to guide you through the profiles.

Responder One had a moderate visual impairment of roughly 70 letters, had two mutations in the Exon 13 of the Ush2a gene, and only received the 50 microgram dose and was followed up for nine months. This patient showed a good therapeutic response on the retinal structure as measured in the ellipsoid zone decline. Showed improvement in the visual field and in the retinal light sensitivity. There was no change in the BCVA. The BCVA was stable.

And Responder Two was much more advanced. Had in the treatment eye only 30 letters. Visual acuity is quite progressed. Had only one Exon 13 mutation and received 100 micrograms. Was followed up for four months. Here, we did not see an OCT retinal structural response, probably because the subject was too advanced in the structural degeneration. Still saw an improvement in the visual field and in the retinal light sensitivity. And also saw an improvement by six to seven letters from baseline for the visual acuity.

So also here, highly meaningful effects. And these are summarized here in graphs. So the effects that I explained to you. On the left hand side, the retinal light sensitivity. The white bar is the treated eye. Remember, everybody received only one injection. There was stability of that light sensitivity in the treated eye, whereas the light sensitivity in the untreated eye declined. And this is the upward curve. So stability in the treated and a decline in the untreated eye.

For the retinal structure, it's the other way around that we see. And that is the wide curve is essentially stable or even slightly improved in the treated eye in white. And the lilac curve shows a slight but steady decline over time, over this up to nine months follow up.

For the visual field and the low luminance condition, we see here a meaningful improvement over the first 12 to 16 weeks and then the decline whereas the contralateral eye, the untreated eye, does not seem to change a lot. Overall, specifically in the visual field, we already see that there may be a dosing interval at this dose level of something like four to five months realistically estimated.

For Responder Two, here are similar pictures. A downward slope for the retinal light sensitivity means improvement, whereas the lilac shows a slight dip in stabilization. So overall, improvement of light sensing in the treated eye with largely stability in the contralateral eye. The retinal structure as measured by the EZ improved in the treatment eye in white in the middle graph and was stable in the contralateral eye. And for the visual field, a similar response in the visual field for the treated eye, as opposed to the untreated eye.

So to sum up the efficacy and share some of our thoughts on the adaptation of the trial while it's ongoing, two out of eight 421a treated subjects demonstrated therapeutic benefit. None of the six sham treated subjects matched the responder criterion. There is early evidence of efficacy at the lower of the two dose levels tested. And this provides further validation of the ProQR platform technology.

The earlier responder data also provides guidance on further adaptation. One logic element is to now look at patients that have two Exon 13 mutations, so-called homozygous. Also treat them with the 100 microgram dose and see if there is an even stronger effect. Because they have the double copy number of mutated alleles that could be subject to the patching by the drug. And also it is of interest to see what happens at the double dose of 200 micrograms.

So what did we achieve? And what is next? So far, there is demonstration of early safety and tolerability. We have seen examples of functional target engagement and benefit. And this is also informing about the dosing interval to be four to five months potentially. We have assessed the utility of various outcome measures. I've shown you the various perimetries here in moderate and advanced disease. And we have now a much better handle on how to apply them in forthcoming trials.

Also about the technical optimization of the protocols and how we look at them. Further, dose ranging is underway. I'm also looking at the effects if you have two mutations on Exon 13. And what we still have to really characterize and manage in the next trial is really the exact contribution of the drug dose and the gene dose, so having one or two alleles. And of course, the durability of the response in those patients that have showed already some benefit and target engagement in the cell

at trial.

Thank you very much for your attention.