

# **ProQR Therapeutics N.V. (PRQR) ASGCT Investor Webcast (Transcript)**

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**Body**

ProQR Therapeutics N.V. (PRQR)

ASGCT Investor Webcast

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Company Participants

Sarah Kiely - IR

Daniel de Boer - Founder and CEO

Gerard Platenburg - Chief Scientific Officer

Conference Call Participants

Jon Wolleben - Citizens JMP

Steve Seedhouse - Raymond James

Presentation

Sarah Kiely

Thank you, and good day, everyone. We appreciate you joining our event today. Today, we are pleased to highlight new preclinical proof-of-concept data for our AX-0810 program targeting NTCP, which was presented yesterday at the ASGCT Annual Meeting in Baltimore. On Slide 2, you'll find the agenda for our call and our speakers. From the management team are Daniel de Boer, our Founder and CEO, who will provide a brief introduction; and then Gerard Platenburg, our Chief Scientific Officer, who will take us through the data presented at ASGCT. Following the presentation, we will have a Q&A session with covering analysts before we conclude the call. Today's event is being recorded, and we will have a replay available on our Web site following the event. You can also find our ASGCT poster under the Publications and Presentations section of our Web site. On Slide 3 is our forward-looking statements. During the call today, we will make forward-looking statements. There are risks and uncertainties associated with an investment in ProQR, which are described in detail in our SEC filings.

I will now turn the call over to Daniel. Daniel?

Daniel de Boer

Thank you, Sarah, and good morning, and good afternoon, everyone. Thank you for joining us today. We are pleased to share an update with you on the data that we shared at the ASGTC Annual Meeting. But first, I'll provide a brief overview of the company's strategy and our proprietary Axiomer RNA editing platform. Axiomer was invented at the ProQR Labs in 2014 and uses the well-proven modality of oligonucleotides to recruit a novel mechanism of action. Axiomer uses editing oligonucleotides or EONs, to recruit endogenous ADAR to edit individual basis in RNA. ADAR is present in all human cells, and RNA editing is a naturally recurring process. In fact, it's happening in all of us right now. Our proprietary Axiomer platform makes use of the ADAR mechanism that nature has developed and recruits it to edit specific nucleotides in a targeted way. Preclinical platform data demonstrate that Axiomer is broadly validated across multiple genes. And today, we'll focus on the preclinical proof of concept for our AX-0810 program, starting NTCP for cholestatic diseases. Our strategy includes both in-house development of pipeline programs, initially including AX-0810 as well as AX-1412, targeting the B4GALT1 gene for cardiovascular disease and using the Axiomer technology for selective partnering and expertise in pathology, like in our partnership with Eli Lilly, allowing us to capture the full value of this platform technology.

ProQR has quite literally led the field of RNA editing since 2014. When ProQR scientists invented the RNA editing technology using endogenous ADAR and for the first experiments using our editing oligonucleotides to recruit natural and endogenously expressed ADARs. These experiments also lead to the first IP filings for this technology back in 2014, which laid the foundation for our leading IP estate today. ProQR holds more than 10 platform patents protecting the use of oligonucleotides to recruit inductions ADAR broadly. Several of these patents have been granted and were subsequently opposed in several jurisdictions, where the patent court ruled in favor of ProQR and upheld the patents. So our foundational IP estate is not only granted, but also tested to position and survives that, which reaffirms the conviction in our leading IP estate. Finally, as we reported in our Q1 financials this morning, I also note our strong cash position, ending Q1 with approximately EUR 103 million, providing a runway into proper mid-2026.

Now moving on to our pipeline on Slide 5. As you will see, our pipeline contains a variety of targets for rare and prevalent disease as well as wholly owned and partner programs. We plan to capture the value of our platform across 2 strategies: first, through the development of an internal pipeline of high-impact medicines; and second, through selective partnering. We're initially prioritizing AX-0810 for cholestatic disease and targeting NTCP -- and targeting NTCP and the AX-1412 program for cardiovascular disease, which targets the B4GALT1 gene. There are a number of earlier-stage programs as well, which we will share more about in due course. We've partnered with Eli Lilly on currently 10 targets on the Axiomer platform, where ProQR release discovery phase and Lilly all phases beyond that. This partnership so far brought in $125 million in upfront payments and Lilly holds an option to expand the partnership from 10 to 15 targets, for which they would pay an additional $50 million in opt-in fee. In addition to this, ProQR is eligible to receive $3.75 billion in milestone payments plus royalties. We are very pleased with the partnership with Eli Lilly and continue to execute on that with high priority. We're also pleased to note that at ASGTC, we actually have a poster together with Lilly on some of the development work we were doing with Lilly. We also earlier this year announced a partnership with the Rett Syndrome Research Trust, which is focused on developing editing oligonucleotides, starting an underlying genetic variance that causes Rett syndrome, a progressive neurodevelopmental disorder caused by genetic mutations in the MECP2 gene. Given the vast opportunity with the platform, we have appetite and capacity to selectively form additional multi-target discovery partnerships.

Moving on to Slide 6. Building on our experience from the last 10-plus years, we have designed a translational strategy that we believe gives a high probability of success for our first in-human trials. Our objectives are to generate data sets in human studies where we are studying editing and disease-relevant biomarkers with proper sample sizing. To do so, we selected targets that introduce a variance in a wild type sequence such that this allows us to study target engagement and biomarkers in healthy volunteers. The advantage is that in a healthy volunteer study, we can, in a much more efficient way, have appropriate sample sizing in each cohorts, get the data set without disease background noise and get to a high-value data set in a short amount of time. The targets are largely derisked because we source these from human genetics research for populations that carry these variants, which are associated with health benefits. So in these trials, we can in a cost- and time-effective manner demonstrate RNA editing or target engagement, disease-relevant biomarkers, corporate PK and dose finding in addition to safety and tolerability.

With that, I'm now pleased to hand over the call to Gerard Platenburg who will take us through our data presented here at ASGCT.

Gerard Platenburg

Thank you, Daniel. On Slide 7, I'm very happy and proud to share a little bit of the data that I presented yesterday at the ASGCT. I'll take you through the background of the ADAR technology as well as the experiments actually done to come up with the [Technical Difficulty] was presented. On Slide 8, you actually see what ADAR editing is. It's an endogenous system where we use ADAR, Adenosine Deaminase Acting on RNA, to execute its natural function of RNA editing and that is to convert Adenosine into Inosine as you can see over here. ADAR [Technical Difficulty] doubled stranded RNA, which you find in natural RNA. And on Slide 9, I actually made a picture where on the left side, you see the natural ADAR editing. We studied that and provided by using oligonucleotides or editing oligonucleotides to bind to the target RNA providing a docking for ADAR as an enzyme and directing its action to a very specific adenosine that we would like to edit. So on Slide 10, you can actually see that we are creating a new class of medicines with a broad potential. There's multiple ways to apply the technology. On the left side, we see the correction where there's many, many G-to-A mutations that we find in monogenic diseases that we can correct. But on the right side, you see a vast opportunity to use in protein modulation. And for that, we can actually think about using ADAR to ultra protein function or to include protective variants that by genetic screens, we find protective variants and alter the function of specific proteins for their protective properties.

We can also use the technology to disrupt and change post-translational modifications such as phosphorylation, glycosylations and many more that we can change. Lastly, we can change protein interactions and that's being used to change localization of protein folding and protein function. So in the next slide, our share data, obviously, that would bring us into altering a specific protein of a protein. So on Slide 11, you see that we are creating AX-0810 for cholestatic diseases where the cholestatic diseases have a high unmet medical need where patients accumulate bile acids in liver leading to fibrosis and ultimately liver failure. Bile acids are very essential molecules for absorption of certain nutrients and vitamins in the small intestine, but if they accumulate in the liver, that can lead to disease. So AX-0810 is a unique therapeutic approach, changing the cause of disease at the site of -- at the hepatocytes. So if you turn to Slide 11 -- sorry, Slide 12, you see that the actual mechanism uses the sodium taurocholate cotransporting polypeptide protein which is encoded by the SLC10A1 gene and it's expressed at the membrane of hepatocytes. And usually, it is there to run the bile they produced in the liver to actually reuptake the bile acids for more than 90% in the hepatocytes. And that's something that is taking place every day. So when the bile ducts are obstructed, we start to accumulate the toxic effects of bile acids in the liver. NTCP is the target for us to actually divert the reuptake of bile acids from the hepatocyte to the bloodstream. So in nature, we find variance that actually have that already that property in them. And those variants specifically have ultra properties that lower the reuptake of bile acids from the hepatocytes of the bloodstream. So the strategy that we follow is a protein sparing strategy where the functions of the NTCP are sales, but the bile acids reuptake is changed from hepatocytes.

So on Slide number 13, you see actually that studying the NTCP protein based on genetic screens, but also in silicone analysis, much has learned of the mechanism of bile acids transport. And as you can see over here, modeling in silicone analysis shows that to be able to transport the bile acid to the central core, you need actually the binding of 2 sodium molecules at its core. That's something that is essential for its function, and that's been studied very well. And if you look at the conserved binding side of the both sodium molecules, we focus on the binding side of the second sodium molecule, and that is to look at the conserved amino acids that were predictive in structural analysis. If you then turn to Slide number 14. If you study the glutamate residue apposition 68, it's very important that, that molecule is over there to provide the context for the binding of sodium, which in itself is essential for the transfer to bile acid. When changed to an arginine, you actually disrupt some of the hydrogen biles that are there, and that's essential that, that disruption no longer allows the binding of a sodium molecule. That, in itself, lead to the understanding that by avoiding the binding of sodium in that specific spot, you lead to an altered uptake -- reuptake mechanism of bile acid, which is shown on the right side of the slide -- in Slide 14, this slide where we studied the reuptake of bile acids in cells where the cells expressed on the mid -- on the wild-type NTCP where you see uptake of the bile acid, whereas the variance, the Q68R is no longer able to take bile acid up to the cell. So the mechanism there shall really that the interaction of sodium is impaired and thereby we impair the uptake of bile acid.

So on Slide number 15, we show data that actually indicates that there's no -- that the QR60R variant only affects the bile acid update, but the presence of the RNA and the protein entity membrane in the middle panel, but also the localization of the protein on the right panel, as you can see in these expressed cells is not impaired. So we only affect the NTCP mediated bile reuptake function. And that is, of course, that we are asking. So on Slide 16, we then incubate cells with our EONs able to edit the target site in the NTCP RNA expressed in these hepatocytes. And as you can see, we see a very nice dose-dependent response for editing mediated bile acid reuptake. So there's a nice decrease after the editing taking place in these cells, which was very relevant, as you can see over here. So having now proven that we found variants that are no longer able to reuptake bile acid, but to maintain the function of the protein itself, we took that into in vivo, where we studied the concept in nonhuman primates on Slide number 17. And this experiment was done to actually show proof of concept to show editing in vivo in the liver, but also to show a correlation between editing and the bile acid uptake alteration. And what you can see here is that increased editing gives rise to a full increase of serum bile as we would expect. So with EON, which is an early generation EON at around 30% editing, we see about a eightfold increase in serum, and that is exactly what we wanted to achieve.

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Slide 18 is that in the next step towards development, we are now generating EONs with further optimize potency, as you can see over here and leveraging the expertise that we have EON design optimization, chemical optimization, we now are developing these molecules with greater effectivity as you can see over here and leading to an at least threefold increase compared to the earlier generation of [Technical Difficulty]. So on Slide number 19, I can show you that there's translatability and clinical relevance of the serum bar as the changes in liver fibrosis. So the actual EONs definitely have generated is confirmed by sequence homology, and we've developed the molecules that we've tested in human cells as well as in non-human primates that are able to execute the action of editing in human cells as well. So the molecule that we've generated in these experiments will go through the next phases of development as well. As you can see over here, there's the serum bile acid of human [Technical Difficulty] plasma, plasma of monkeys and at this editing experiment in non-human primates, you see a very nice increase of serum bile acid concentration at several days. And what is very encouraging is that we find a naturally occurring variants in humans, where these humans carry a variant that is actually no longer able to reuptake bile acid into the hepatocytes, that in the plasma with very high total bile acid levels. It is not harmful as the evidence by the data here. So we feel very much encouraged by the data that we now have, and we're looking forward to the next steps in the [Technical Difficulty].

So summarizing on Slide number 20, we see a first proof of concept to alter NTCP in non-human primates in vivo. For the first time, we show target engagement as well as biomarker change in the bloodstream using Axiomer EONs. We have a very specific targeted approach to specifically modify the [indiscernible] protein resulting in ultra bile S3 uptake in cholestatic diseases as this data supports are moving forward into an application into a therapeutic application in cholestatic disease. So with that, I'd like to give the word back to Daniel.

Daniel de Boer

Thank you, Gerard, for walking us through the data. On Slide 22, with this preclinical proof-of-concept data sets in hand, we are moving this program forward towards an entry into the clinic around the end of this year or early next year. As part of our platform clinical validation plan, we are designing our initial trials in healthy volunteers to benefit from a clean data set with no disease background noise, proper sample sizing and rapid execution. With these programs, we can as well measure RNA editing, target engagement and disease relevant biomarkers. This trial will have a typical single [Technical Difficulty] dose, multiples [Technical Difficulty] dose design, allowing us to generate a valuable translational data set for development of AX-0810 in cholestatic diseases. Further details about the trials we will share in the second half of the year. On Slide 23, with this exciting data presented at ASGTC and on the call today, we look forward to sharing the translational data on our clinical candidate for AX-0810 with you in the second half of the year as we prepare for our entry into the clinic around late '24, early '25. Over the course of this year, we will also share with you preclinical proof-of-concept and translational data on our second clinical program, AX-1412, circling cardiovascular disease via B4GALT1 gene.

We will also provide further platform updates and potentially additional pipeline programs. We are progressing with our Rett program, which is in partnership with the Rett Syndrome Research Trust, and we will share more information on this program as we progress. And as we announced in our quarterly release this morning, we have achieved the first milestone in our Lilly partnership and anticipate many more to follow, including this year. We do anticipate to potentially enter into an additional multi-target discovery partnership. And on the IP front, we will continue to file additional IP and continue to enforce our leading IP estate. With our cash on hand, we are funded into mid-2026, well beyond all the key value inflection points and with ample opportunity to extend the runway from non-dilutive sources. With that, operator, we are now ready to take questions.

Question-and-Answer Session

Operator

[Operator Instructions] And your first question comes from the line of Jon Wolleben from Citizens JMP.

Jon Wolleben

Congrats on the data and progress. Wondering if you could talk a little bit about the translatability between the in vitro and in vivo editing because you gave us a nice increase in the optimized EONs versus that the poster, which is the first generation. So just wondering what you would expect to see with in vivo letting with the optimized EONs?

Daniel de Boer

I'm going to pass it on to Gerard.

Gerard Platenburg

I would anticipate that the more improved editors would give us higher editing in vivo as well. I think the improved, let's say, version of the molecules not only give us a higher absolute level of editing, but also the, let's say, we need less molecules to create that editing basically. So I would expect the molecules that we are developing will give rise to higher editing in the -- in subsequent animal studies.

Jon Wolleben

And you talked a little bit about target editing range in the past. Is that across the board what you'd want to see, if you could remind us or if this is target or disease area specific? And then last one for me. Is this GalNAc delivered? And is there any difference between delivery on what you did in these non-human primates and what you expect in your clinical candidate?

Gerard Platenburg

I think important is to note that we feel that the fold increase that we see and also the absolute levels that we see bring us in the range of clinical applicability is known from the -- from literature is expected as a change of a twofold in serum bile acids could lead to a clinically meaningful improvement. So obviously, we need to show that, but that's something that is in the realm of possibilities So on your second question, we are -- clearly, this was to show proof of concept of the AX-0810, but we are testing different modalities in our IND-enabling studies, and we'll announce the development candidate later this year. So for your information, we are looking at GalNAc and LNP formulations amongst others.

Operator

Your next question comes from the line of Steve Seedhouse from Raymond James.

Steve Seedhouse

First, just wanted to ask about bile acid synthesis with this mechanism. Is it increased to compensate for the reduced reuptake? And what do you think chronic treatment would due ultimately to the bile acid pool as a monotherapy? And then is this something that you maybe want to combine with like an [Technical Difficulty] or think about managing the serum bile acid pool long term holistically?

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Daniel de Boer

So we know that in nature, this variant occurs. There's people that have this variant an NTCP that's how we came across this approach. Those people represent themselves without any disease manifestation. So they have high concentration of bile acids in blood, but do not represent any clinical symptoms as a negative downside of that. So in many ways, nature has already done the experiment for us to show that this variance in NTCP will not give you a negative side effect of the increased bile acids. We also know from literature that this variance increases the excretion of bile acids from blood through both ceases in urine. So there is also a regulation of eliminating the bile acid from that.

Steve Seedhouse

So in the poster, like the increase in serum bile acids corresponding to editing, I just -- in a clinical study, I guess, where like serum bile acid -- reduction in serum bile acids has been an endpoint than cholestatic diseases, for instance. Could you still use that with chronic treatment? Or would you expect an increase? And how you -- like how will this sort of feature of the mechanism effect the way you think about clinical development and trial design and regulatory strategy in various cholestatic diseases.

Daniel de Boer

So the IBAT approach is obviously a very different therapeutic strategy. I think with NTCP targets, we can go to the core of the problem, which is the concentration of the bile acids in hepatocytes and presented that concentration gets too high to provide -- to prevent liver fibrosis. I think with this different therapeutic strategy, we will likely be looking at different endpoints and measuring different things. That also depends a little bit on the indication of choice that we will choose once we go into patients. And we have a little bit of time to determine how to go about that. The first objective here of these trials is to prove RNA editing in human in a clean data set in a robust way with proper sample sizing to set us up for proper patient trials after that.

Steve Seedhouse

And then just on one of the details of the trial design that you pointed out, looking to detect RNA editing and circulating exosomes, what's your confidence in just the precision and the accuracy with which you'll be able to -- and just the sensitivity of that test to be able to measure RNA editing. Do you have some evidence or some reasons for sort of high confidence that you'll be able to detect that in pretty readily in the exosomes?

Gerard Platenburg

So the actual test has been pioneered by folks at Alnylam. So the accuracy of the test itself is highly dependable on the end feasible, so to speak. So we have a different mode of action, obviously. So they're determining the sensitivity and the reliability of the assay as we speak right now. But it will be the idea of that similar to what they found that they can measure the effect. The target engagement at the RNA level as what they have published.

Steve Seedhouse

Last question, if I could, just the delivery methods you're thinking about for the human clinical programs, just in the RNA editing field, I mean, there's some work with LNPs, GalNAc, AAV. How are you thinking about the sort of near and long-term optimal approach to delivery of the editing oligonucleotides?

Daniel de Boer

So we're exploring both LMPs and GalNacs and some other things. We are not exploring viral delivery. And for this program, in particular, we have kept our options open. So in our IND enabling, there's different delivery moieties that allow us to make a data-driven decision later on in the preclinical development before we enter the clinic around the end of this year or early next year. So yes, we are stepping into proven delivery moieties in this case, GalNac and LNP, and we make our decision later on in the process.

Operator

Your next question comes from the line of Yigal Nochomovitz from Citi.

Unidentified Analyst

This is Ami on for Yigal. We had a couple. First, just looking at the Slide 17 graph, which shows the serum bile acid versus the editing levels. We see meaningful increases in the serum bile acid above 25% editing? Is there a minimum threshold of editing that you believe you need to see that it could result into a meaningful improvement in the disease condition? That's the first one. And then on the second one, what can you tell us about the safety signal that you have seen in the NHP model that you studied?

Daniel de Boer

So we're happy to address this. So we've done -- these experiments were not done to explore the highest editing or really study safety. But really what we've done here is we collected data from a number of experiments where we used different doses and different delivery moieties to study the correlation between editing percentage and bile acid -- total bile acid in serum. And that's the data you see here. So this essentially is the proof of concept that if you edit NTCP, you will get a disease-relevant biomarker change in total bile acid. We do anticipate that these levels will be sufficient. We've been saying, yes, somewhere around 25% editing should be enough to have a meaningful clinical effect and it seems that we have quite some wiggle room there from the data as we have generated. Sorry, your second question was -- yes, on safety. This study was not specifically designed to study safety. But obviously, we're monitoring that, and we've not seen anything out of the ordinary. These are Typically, LNP delivers EONs, single-stranded EONs, and they have all similar profiles. We've not seen anything out of the ordinary. We are now in IND-enabling studies that's obviously where we will further validate and confirm that. But no surprises so far.

Operator

[Operator Instructions] There seems to be no further questions at this time. I would now like to conclude today's conference call. Thank you all for participating. You may now disconnect.

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