ProQR®

# ANNUAL REPORT 2018

*Future medicines in sight*

UNMET NEED IN RARE DISEASES

# AN EYE ON THE GOAL

At ProQR, we focus on areas where there remains significant unmet need for new treatments. For most people living with rare genetic diseases, there are no therapies available. This may be due to the rarity of their disease or difficulties in treating with conventional methods. We hold a strong belief that people with rare diseases should enjoy a high quality of life and be able to enjoy it with their loved ones. Over the last several years, this goal has brought many good things to us, and the people we aim to help using our RNA therapies. In this magazine, we want to highlight what we have worked on and achieved in 2018, but also provide a glimpse into what 2019 will bring.

In recent years we have focused more on eye diseases. The reason for this is two-fold as most genetic eye diseases don't have a treatment and RNA therapies are well suited to treat these types of diseases. This focus has yielded results such as our positive clinical data for sepofarsen (formerly named QR-110). Sepofarsen is being developed for people with Leber's congenital amaurosis 10 (LCA10). LCA is the most common genetic cause of childhood blindness of which LCA10 is one of the most severe forms affecting about 2,000 patients in the Western world. In LCA10 a process called photo-transduction is disrupted in the light detecting cells (photoreceptor cells)

*Every minute of every day,* **TEN CHILDREN AROUND THE WORLD** *are born with a rare genetic disease*

in the retina, due to a mistake in the CEP290 gene. The mistake, or mutation, changes the CEP290 protein so that it cannot function properly causing poor vision and blindness. Sepofarsen is our effort to repair the mutation in the RNA, resulting in a normal protein to improve vision. In September of 2018, we presented interim results from the ongoing Phase 1/2 clinical study demonstrating that most participants experienced vision improvement following treatment with sepofarsen. It's really encouraging to see beneficial results for patients in the first study, which we plan to finish in 2019. Additionally, we are also planning to start a Phase 2/3 clinical study for sepofarsen called ILLUMINATE. The ILLUMINATE trial has the potential to be the final study required for market approval for sepofarsen. Read more about this in our interview with Dr. David Rodman, Executive Vice President of Research & Development at ProQR.

Another big development is our investigational therapy for Usher syndrome type 2. Usher syndrome is a devastating disease combining deafness and blindness. There are three types, which are determined by the severity of hearing loss, the presence or absence of balance problems, and the age of onset of symptoms. Type 2 is caused by a DNA mutation that results in a lack of usherin protein, resulting in retinitis pigmentosa (RP) that disrupts eye function. Our drug QR-421a circumvents the mutation by skipping over the mutated part of the gene. This generates a shorter yet still functional usherin protein, with the aim to stop or even reverse the vision loss. As a therapy, it would complement the cochlear implants that help mitigate most of the hearing loss these patients experience. We are proud that 2018 saw the start of preclinical testing of QR-421a, and even more proud that we partnered with Foundation Fighting Blindness (FFB). The $7.5 of million funding provided by FFB for the clinical development of QR-421a is more than just monetary support but a vote of confidence in our patient-centric drug development approach. We aim to publish interim results from the Phase 1/2 clinical study of QR-421a, called STELLAR, in 2019.

We are also working on another therapy for RP, caused by a different mutation called autosomal dominant retinitis pigmentosa (adRP). This disease is related to the light-sensitive protein rhodopsin, which transforms light into neural signals for the brain. In patients with adRP this function is impaired. Our drug candidate, QR-1123, aims to block the formation of the mutated rhodopsin protein, potentially stopping or reversing vision loss. QR-1123, which was initially discovered by Ionis pharmaceuticals, was obtained by ProQR with an exclusive worldwide license. In 2019, we are planning to start a Phase 1/2 clinical study for QR-1123.

### Butterfly Wings

While we are excited about our progress in ophthalmic diseases, it's by no means the only path we are exploring. The effort we started in dystrophic epidermolysis bullosa (DEB) is continuing to progress. DEB is one of the more severe forms of EB, caused by a weak connection between the dermis (inner layer) and epidermis (outer layer) of the skin. This connection is weakened

by a DNA mutation that inhibits the connective function of the protein collagen (type VII). It results in the blistering of skin and mucosal membranes. Those affected have to live with constant pain, infections and risk of malnutrition. Because their skin is as fragile as a butterfly, children with DEB are sometimes called 'butterfly children.' It's a heart-breaking disease and so far only palliative treatments are available.

At ProQR we discovered an investigational drug called QR-313 for a subgroup of DEB patients. By skipping the disease-causing mutation, a shorter but functional collagen protein is expected to be formed. This should result in better wound healing and prevent blistering. In 2018, we started the first clinical study (Phase 1/2) for QR-313, called WINGS. A newly formed company, Wings Therapeutics, dedicated to developing therapies for DEB will continue development of QR-313 and complete the WINGS study.

### Financial sustainability

Looking back at 2018, there are also financial reasons to be encouraged with our progress. We started the year with €48.1 million in cash and throughout the year have been successful in raising capital to fund the development of all the programs that can potentially have a meaningful impact on patients. At the beginning of 2018 we received the already mentioned $7.5 million from the Foundation Fighting Blindness. In addition we were granted approximately $5 million from EB Research Partnership and EB Medical Research Foundation to develop QR-313 for patients with dystrophic epidermolysis bullosa.

In September, we finalized a successful public offering of ProQR shares. We sold 6,612,500 shares at $15.75 per share, raising approximately $104 million. And to close the year, in December we were granted €5 million from the Dutch government as innovation credit for the development of sepofarsen. With all this, we ended the year with €105.6 million in cash, which will fund the development of four of more clinical programs, including the potentially pivotal trial for sepofarsen and advance our early stage pipeline, providing a cash runway into 2021. ■

## 5-YEAR PLAN: ProQR'S VISION2023

We have always set ambitious goals to help as many patients as possible using our RNA therapies. In the coming five years our aim is to build out our platform for the discovery and development of programs in eye diseases in order to have marketing approval for at least two programs and have three additional programs in late stage clinical studies by the end of 2023. Beyond that we plan to have at least seven additional programs in our pipeline. In order to bring our medicines to patients as efficiently as possible we intend to independently commercialize the eye programs in our pipeline. Most of our pipeline will be focused on eye diseases because we think this is where we can have the biggest impact, but we plan to also develop programs in other areas where there is a strong need for new therapies, such as skin and brain diseases. ■

**2 COMMERCIAL PRODUCTS**

**3 LATE STAGE PROGRAMS**

**7 EARLY STAGE PROGRAMS**



## RESEARCH AND DEVELOPMENT PIPELINE – DECEMBER 2018

### Ophthalmology

| DISCOVERY | PRECLINICAL DEVELOPMENT | PROOF OF CONCEPT TRIALS | LATE STAGE/ REGISTRATIONAL TRIALS |
|---|---|---|---|

- **Sepofarsen (QR-110) for LCA10 p.Cys998X**
- **QR-421a for Usher syndrome 2A exon 13**
- **QR-1123 for P23H adRP - discovered by Ionis**
- **QR-504 for FECD3**
- **QR-411 for Usher syndrome 2A PE-40**
- **QR-1011 for Stargardt's disease c.5461-10T>C**
- **QRX-461 for Usher syndrome undisclosed mutation**
- **QRX-136 for LCA undisclosed mutation**

### Beyond ophthalmology

| DISCOVERY | PRECLINICAL DEVELOPMENT | PROOF OF CONCEPT TRIALS | LATE STAGE/ REGISTRATIONAL TRIALS |
|---|---|---|---|

- **QRX-704 for Huntington's Disease**

*For the latest developments in our pipeline visit www.proqr.com/pipeline/ or scan the QR-code on the back of this magazine*

AT A GLANCE:

# WHAT ARE RNA THERAPIES?

RNA therapies: it's what we do, but it can sometimes sound complicated. If you want to learn more – keep reading. Here we'll explain how cells function, and how RNA therapy can intervene in genetic diseases.

DNA lies at the core of normal cellular function. It contains genes, which are the genetic instructions on how to make the functional building blocks of the cell, such as proteins. However to get from the DNA to protein, the information in the DNA is first copied into RNA. The RNA acts as the blueprint for making proteins. Proteins are responsible for making sure that the cells in your body function normally.

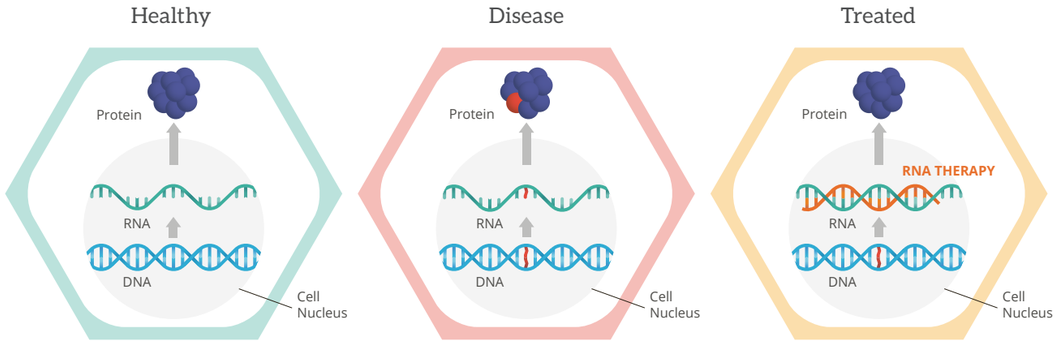
Genetic diseases are caused by mistakes, or mutations, in the DNA. These mutations are copied into the RNA blueprint, which means the protein is also not made correctly. Malfunctioning proteins can cause cells to not function properly causing the disease. For example, if an essential protein is not working in the eye this may lead to blindness.

We take an innovative approach to treating genetic diseases.

Using RNA therapies, which are basically short pieces of RNA made in a laboratory, we aim to repair the RNA blueprint to restore the function of the protein. This way, we can target the underlying cause of the disease without making permanent changes to the DNA. Scientists around the world, including those at ProQR, have developed a toolbox of novel ways to repair RNA. As a result, depending on the type of mutation, we can choose the best tool to do the job. ■



## ProQR RNA MEDICINE PLATFORM
*(human cell)*




*Check out the video on www.proqr.com/we-are-proqr/ if you want to learn more*

## OUR TOOLBOX OF RNA THERAPIES

At ProQR, we use different types of RNA therapies, depending on what type of mutation causes a disease. Together, these technologies form our 'toolbox' to repair RNA. Here they are explained in a nutshell.

**Splice correction**
Sometimes a mutation causes the cell to incorrectly splice the RNA, either leaving behind parts of RNA that should have been cut out or cutting out parts that should have remained. An RNA therapy can be designed to 'hide' the mutation that allows the cell to splice the RNA correctly and restore the function of the protein. This is how sepofarsen for LCA10, QR-411 for Usher syndrome and QR-1011 for Stargardt's disease are designed to work.

**Exon skipping**
A mutation that causes a disease can sometimes be repaired using the exon skipping method. An RNA therapy can be designed to cause the cell to 'skip' the part of the RNA (the exon) that contains the mutation so that the rest of the RNA can still make a protein. The protein is a little shorter than normal, but can still perform its function. This is how QR-421a for Usher syndrome is designed to work.

**Mutant-specific knockdown**
People inherit two copies of each gene, one from each of their parents. Sometimes, a mutation in one version of the gene leads to a toxic protein that causes a disease. It is possible to design an RNA therapy that only destroys (knocks down) the mutated version of the RNA. The toxic protein is therefore not made and the cause of the disease is removed. This is how QR-1123 for adRP is designed to work.

**Repeat targeting**
Sometimes a mutation causes a stretch of DNA to be copied a few times, these copies are also present in the RNA. This is called a 'repeat', and may cause disease by creating a toxic RNA or protein. An RNA therapy can be designed that targets and blocks the toxic function of these repeats to prevent their negative effect. This is how QR-504 for FECD3 is designed to work.

**RNA editing**
Scientists at ProQR have developed a completely novel technique to repair RNA. An RNA therapy can be designed to actively recruit the cell's own RNA editing system which can edit certain mutations in the RNA back to its healthy form. This technique is used for ProQR's Axiomer® platform that can potentially be used to repair thousands of disease causing mutations. ■

**DAVID RODMAN**, EXECUTIVE VICE PRESIDENT
RESEARCH & DEVELOPMENT

# TOWARDS A THERAPY FOR ONE PATIENT

It has been roughly two years since David Rodman became the Executive Vice-President Research & Development at ProQR. He was appointed to apply his knowledge of study design and genetic diseases on our pipeline. In September of 2018, we were able to present positive interim results from the clinical study for sepofarsen, our potential therapy for Leber's congenital amaurosis 10 (LCA10), a genetic disease causing blindness in childhood.

*"After two weeks he called his doctor and said* **HE WAS ABLE TO READ SIGNS"**

How did you feel when you got the results?

"My feelings can be best described by talking about one of the patients, a 42-year old fella who had been born with LCA10. Within years of birth he was already down to just tunnel vision, but he was still able to read and function with glasses until his early twenties. By the time he entered the study, he could only distinguish light from dark. We then gave him the treatment, and when he came back after four weeks he was able to see bright lights in different colors. He was scheduled to come in another month, but after two weeks he called his doctor and said he was able to read signs. That was something he hadn't done in twenty years. Then when he came in for his second treatment he was reading letters on an eye chart, for the first time since he was a kid. That's tremendous. It was great for the company too, because it's really fortunate to see everything we work for come together so early on in the process.

We did this study with 11 patients and got very consistent responses, so we're going to move to the next phase. We will start a seamless adaptive Phase 2/3 clinical study that could be the last study we have to do before we get market approval. That it's an adaptive study means that we can adapt the design as we go, based on what we learn. This makes it a modern study design that has been done before, but it's the first time it would be applied in an eye disease. With rare diseases and small patient groups it's essential to be flexible in study design, and thankfully the regulators are enthusiastic and willing to listen."

Seeing the success of sepofarsen, what's your vision for ProQR in eye diseases?

"We're at a stage now where we want to go both narrow and deep. Now that we've shown that our RNA therapy had an effect on LCA10, we want to exploit that. We are doing an extensive search to make an inventory of all genetic eye diseases, and select the ones that can be fixed using our toolbox of RNA therapies. This would give us a theoretical playing field. At the same time, we need to learn more about patients, because a lot of people with vision problems don't know what genetic mutation is causing their disease. This is why we work with foundations like Foundation Fighting Blindness who provide genetic testing to patients. We could probably end up with a list of hundreds of diseases that we could potentially target, but then we have to prioritize.

The eye is a very good treatment area for RNA therapies. One major issue with RNA therapies in general is that it's difficult to deliver it intact

## SEPOFARSEN (QR-110) FOR LEBER'S CONGENITAL AMAUROSIS

LCA10

Lose sight in first years of life

p.Cys998X mutation affects **~2,000** patients in the Western world

SEPOFARSEN

Locally administered in the eye. Routine procedure

Anticipated infrequent dosing of 2 times a year

Goal: Restore vision/ prevent vision loss in patients with LCA10

## QR-421A FOR USHER SYNDROME

Develop hearing and vision loss in childhood and are completely blind by mid adulthood

USH2A exon 13 mutations affect **~16,000** patients in the Western world

## QR-1123 FOR P23H ADRP

P23H ADRP

Progressive reduction in night & peripheral vision. Blindness is frequent in mid-adulthood

**~2,500** patients with P23H adRP in United States

QR-1123

Locally administered in the eye. Routine procedure

Anticipated infrequent dosing of 2 times a year

Goal: Restore vision/ prevent vision loss in patients with P23H adRP

*"We could end up with a list of* **HUNDREDS OF DISEASES** *that we could potentially target"*

to the relevant tissue, but in the eye this problem doesn't exist. We can just inject it into the liquid in the eye, actually a common procedure that is used for many drugs nowadays. The RNA therapy then automatically spreads and enters all of the retinal cells, where it can act. Another reason is that we have a very good and novel system to test potential therapies in. We can take stem cells from a patient's skin and grow these into 'retina in a dish', what we call the optic-cup organoid model. This means we can test drugs in a very relevant setting, and the results suggest that it can predict what the drug can do in the real eye. A nice benefit is that these organoid models reduce the need for animal testing too.

Besides looking narrowly at LCA, we are also taking a broader perspective on retinal diseases. For example, we have started a clinical study in patients with vision loss due to Usher syndrome. This disease is the most common cause of combined deafness and blindness. This drug, QR-421a, uses exon skipping, a different mode of action to hopefully restore the vision loss that these patients experience. We are expecting to report the first results from this study in 2019."

For another eye disease, autosomal dominant retinitis pigmentosa (adRP), you have licensed a program from Ionis. What's the story there?

"There are a few reasons really. Firstly, adRP patients go through a stage of tunnel vision and ending with complete blindness and there is no therapy available to them. This made me enthusiastic about trying to make a difference. Secondly, the disease progresses more slowly which means that measuring the effect of the disease and the therapy takes a long time. Ionis, the partner that discovered the drug, had just followed a group of patients closely for two years to map the progression. We can now use that knowledge and save time in testing the drug. This helps the patients quicker. The third reason is that the disease is caused by a very different type of mutation than we have thus far targeted. The type of RNA therapy is therefore different too, which gives us a chance to learn to work with it.

Instead of repairing the RNA like we do for LCA and Usher, in adRP, we are trying to selectively break down the mutated version of the RNA that creates a toxic protein, and not the healthy one.

The work on adRP also made me realize that with such subtle differences, we need to rethink what we measure in our clinical study too. What actually matters to the patient? I think we should measure, for example, if a therapy lets them run an errand quicker, or allows them to drive a car. We are also exploring the possibilities of virtual reality for this.

Our aspiration for eye therapies is that we want to start at least one new program a year, for the foreseeable future. Once we get the first programs I just described done, and we've established the potential of RNA therapies in the eye, then the next step is to get to what we call N=1 studies. To scale down from rare diseases with a few thousand patients in the world to diseases with only hundreds and, finally being able to treat versions of the disease that are so rare that it affects perhaps just one patient in the whole world. Obviously, this will blur the boundary between study and treatment, so we need to find a way to treat individual patients with a new drug in a safe way while tracking their well-being. Once we have figured that out, we will be able to help a lot more patients." ■

**MAARTJE**, LIVING WITH USHER SYNDROME

# I WANT MY DAUGHTER TO BE ABLE TO DREAM, AND KEEP DREAMING

At a glance, it's hard to tell Maartje de Kok – 41, married and mother of four – has Usher syndrome. Though she manages her life very well, it took her a long time to get to that point. "I have learned to be optimistic, but the sombreness is always there."

Maartje lives in a brand new house with her husband Peter and her kids Amber (11), the twins Ingmar and Jente (8) and Kiki (6). She has a job as a social worker, helping parents who have children with a visual handicap. Together with Peter she manages her household quite effectively, and last summer she even gave back the guide dog that she had had for seven weeks. "It was the sweetest dog, but it just felt like an extra child. Every time I finally had some time to sit down, I had to walk the dog. It's just better this way."

To an outsider it might not be immediately obvious that she has Usher syndrome type 2, and that her field of vision is only six degrees, instead of 180. But it's something she has struggled with for a long time. "I knew for sure when I was 19, although my ophthalmologist had her suspicions when I was 15. I got hearing aids when I was 2.5 years old already, but only in hindsight was it obvious that my eyesight was deteriorating as well. I couldn't play games in the dark during school camp when I was 12, and I once fell off the stage during a school musical because somebody turned off the lights before I reached backstage. This night blindness slowly progressed until it affected my vision during the day too. By the time I was 15 I was an avid netball player, playing in the highest junior team. But then during the summer I did a lot of reading in the sun without sunglasses, and my vision got worse quite quickly. Because of my experience and talent I was able to compensate for a while, but in the end I had to stop playing netball. It was the same with going out; I had trained myself to memorize the route to the bathroom in a bar, for example. And when we cycled home in the dark I would just focus on the markings on the bike path or the lights in front of me."

As she got older, Maartje struggled with the new reality of losing both hearing and vision. "I used to have terrible nightmares when I was adjusting to the idea of having Usher, and I've suffered two burnouts and struggled with depression. Before I got the diagnosis I felt like I was ready to spread my wings and make something of my life, but then it got taken away from me."

Maartje managed to obtain a degree in social work and was involved in setting up a foundation for Usher syndrome, informing people about life with Usher and raising funds for scientific research. "With our campaigns we stimulate young patients to 'come out of the closet,' and create awareness" she says. "It's important that we start understanding the disease. For this reason the Usher syndrome foundation supports the CRUSH study at Radboudumc in Nijmegen, the Netherlands. The study and accompanying database should uncover how the disease progresses."

A few years ago, Maartje spent two weeks hiking the pilgrim's path to Santiago de Compostela. During those weeks she was challenged in new ways. "A buddy accompanied me to guide me through the hills. Every day we slept in a different place, which meant every day I had to learn new routes to the bathroom and exits. I managed very well though, and applied all kinds of tricks. It was a healing experience, and I found a lot of calm."

She also found a renewed ambition to work, to be productive and to use her education. "I thought to myself 'Let's say I have ten years of vision left. What can I do?' and decided to do a writing course and get a job. What I really rediscovered, I should say, is my dreams. I dared to look into the future again."

A therapy is something she thinks about with some ambiguity. "It's scary to allow hope into my life, because everything has always been about things getting worse. And I've heard promises from doctors and researches before – we were going to have a cure in 10 years, and that was 20 years ago. On the other hand, one of my daughters has Usher syndrome too. Jente is eight years old, and she still has so many milestones ahead of her. With Usher syndrome the clock is really ticking; if there is a therapy before she's 15, she might be able to keep playing netball, which she enjoys just like I did. If the therapy comes when she's 18, netball and driving a car might be out of the question but riding a bike or studying might not. And it goes on like that. That's the time pressure that we're under. I know how Usher narrows life's path of choices, and I don't want that to happen to her. I want her to be able to dream, and keep dreaming." ■



*"I have learned to be optimistic, but* **THE SOMBRENESS IS ALWAYS THERE***"*

**SEDA YILMAZ-ELIS**, ASSOCIATE DIRECTOR
BLACK BOX INNOVATION

# EXPLORING THE POTENTIAL OF RNA THERAPIES



At ProQR, we want to attract talented scientists to take the field of RNA therapies to a higher level. For Seda Yilmaz-Elis, working in this field was the only thing she wanted after finishing her PhD. Now she works in our Black Box Innovation group, identifying the RNA therapies of tomorrow.

*"Working as a scientist at ProQR is basically* **MY DREAM JOB**"

Seda came to the Netherlands for her PhD, which she did on the application of RNA therapies (antisense oligonucleotides), at the Leiden University Medical Center. "After that I was in love with RNA therapies," she recalls. "It was new, it was very innovative, and I still think it's the therapy of the future. I also liked the translational applicability of what I was working on. You do something in the lab, and you can see the results in the patients later; from bench to bedside, that is extremely motivating. So when I completed my PhD, I wanted to continue in this field and working as a scientist at ProQR was basically my dream job."

Fast forward a few years, and Seda made her dream come true – she started working at ProQR as an Associate Director and project leader.

### Why do you like RNA therapies so much?

"They can do the same job as conventional drugs, but have broader applications. If the disease is the result of an error in the DNA, an RNA therapy can often fix it. For example, they can be designed for a specific mutation, so it's potentially really personalized medicine. The therapy works with short pieces of RNA, called antisense oligonucleotides, it's relatively easy to manufacture once you know what it needs to look like."

### But what about other methods like gene editing and gene therapy?

"The advantage of an RNA therapy is that we can take away the underlying cause of the disease in the RNA, without permanently changing the patient's genetic material, or DNA. This makes the treatment reversible compared to gene editing or gene therapy that make the changes for life. Secondly, antisense oligonucleotides do not usually require complex delivery systems, like viral vectors for gene therapies. In most cases we can deliver it as a 'naked molecule' and it will reach the cells. This makes manufacturing and testing a lot easier."

### Your job at ProQR is in the 'Black Box Innovation' department. That sounds exciting, what is it?

"Yes, it is super exciting! In a nutshell, we aim to find new applications for ProQR's toolbox of RNA Therapies. ProQR works on a number of diseases and therapeutic areas like the eye. In the Black Box we have a broader approach. We try to find new diseases and even completely new therapeutic areas that can benefit from RNA therapies. While we investigate, we always keep an eye out for rare diseases, and target the 'undruggable'. This is risky of course, but I like to root for the underdog."

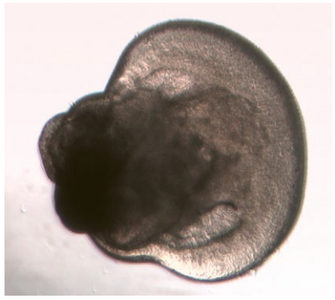
### How does that work?

"First we try to identify a genetic disease, its gene and mutation(s).

# *"It is risky, but I like to root for the* **UNDERDOG***"*

## ORGANOID MODELS FOR OLIGONUCLEOTIDE TESTING

ProQR uses organoid models to test the candidates for RNA therapy. An organoid model is a simplified organ grown in a laboratory, using live human cells. They are made by extracting stem cells from the skin of patients with the disease that the therapy is aimed at. These stem cells can be triggered to become an organ of choice – for example an eye. When successful, these stem cells create a simplified eye, called an optic cup. They can then be treated with the drug candidates, and the results can tell you something about whether the therapy will work. The great advantage of this approach is that we can predict earlier if a therapy can be successful, reducing cost and time. Another benefit is that these models reduce the need for animal testing. ProQR currently has these models in place for skin and eyes. ■



*Retinal organoid in development*

We are looking for genetic defects that can potentially be solved by our RNA technology. We then design an antisense oligonucleotide, which is a short piece of RNA that might be able fix the issue. The design is done 'in silico', which means on the computer, using databases and software. The design is only the start, the next step is finding out which configuration of the design works best. This is done by screening many similar designs in cell cultures. The screening will give us a first impression of the therapy's potential to improve the disease. It helps a lot that we can do our own oligonucleotide manufacturing in-house, which makes it quicker and more cost-effective to test hundreds of candidates in order to find the most effective one.

When we have selected the best candidates, we can go to the next phase of testing. The models we use for this are very sophisticated. We can for example take stem cells from a patient with the disease we want to target and grow the cells into mini organs called organoids. Our ophthalmology group lets those cells develop into simplified eyes which allows us to predict if the therapy would work in the actual eye of that patient. We also do initial tests to see if the therapy is safe. Then, when all the tests are done and positive, we hand the best drug candidate over to the clinical department to prepare it for clinical studies to test the therapy in patients."

### Do you do all this by yourself?

"No, it's always a team job and I'm glad I have a great team with very dedicated and motivated people, everybody has his/her own expertise and we also work in close collaboration with the other teams within ProQR. Luckily we have a lot of expertise in-house but when we need expertise from outside we also cooperate with the expert groups at the universities or with other companies depending on the need."

### After four years, is it still your dream job?

"Yes! ProQR is a very nice organization to work in. We are a very dedicated group of people that put a lot of effort into making patients' lives better. Within the company, there is always room for improving your skills, learning new things every day. The open culture with very little hierarchy creates an atmosphere where everybody can freely reach out to each other. So when you have an idea it's easy to get people to listen, which is critical when you want to innovate." ■

**STEPHEN ROSE**, CHIEF RESEARCH OFFICER
FOUNDATION FIGHTING BLINDNESS

# WE PUSH FOR THE BEST RESEARCH, SO THAT PATIENTS BENEFIT THE MOST

The work we do at ProQR would not be possible without the help from patient organizations and foundations. One of our main supporters is the Foundation Fighting Blindness (FFB), who generously provided 7.5 million dollars of funding for the clinical development of QR-421a, our drug candidate for Usher Syndrome. We checked in with Stephen Rose, Chief Science Officer at FFB, to talk about their perspective.

### The Foundation Fighting Blindness is a strong force in research funding when it comes to blindness. How does the foundation approach this?

"With everything we do, the interest of patients is our top priority. We actually are the world's leading private funder of inherited retinal disease research, spending



*"It* **DOESN'T STOP** *after granting an application for funds"*

20 to 30 million dollars a year on research and clinical trials. But that doesn't mean much if patients don't benefit from it. So we select carefully and try to bring research into blindness and retinal degeneration further. To achieve this, we have an application process for our grants, and pull in outside subject experts from all over the world to help us select the best ones. We really want to pick groups and companies that have a good chance of succeeding.

As Chief Science Officer, it's my personal job to facilitate the ongoing research, to tackle upcoming problems and to make sure we get optimal results. Because it doesn't stop after granting an application for funds. We keep pushing for the best preventions and cures, so that blind people benefit the most.
If we don't get the most bang for our buck, it's just a waste of funds."

### What kind of collaborations do you pursue?

"If you talk about research focus, we don't believe in any particular type of drug. The diseases causing blindness are as diverse as the mutations that cause them, and there is no silver bullet that will take care of it all. We therefore consider gene therapy, gene editing, RNA therapy – they all have potential. We also look at other diseases for inspiration. Take Parkinson's disease or Alzheimer's disease for example. These are brain-related, so they are based on neurobiology just like retinal diseases. The eye is the window to the brain and as such, understanding neurobiology has implications for both brain and retinal diseases.

In terms of partners, if it's companies for the clinical development, we aim for parties that have a proven track record in safety, and that have been able to bring something to the clinic or even the market.
When it's researchers we scrutinize their science. We want the scientists we support to succeed. The group in Nijmegen, at Radboud University, is a good example. They belong to the best groups in the world, and have been an FFB center for years, receiving many investments from us. We actually funded their research that is now being taken to the clinic by ProQR as sepofarsen, which has gotten some very nice results. Still preliminary, but looking very promising. It's important to get that proof of concept. Now we know that RNA therapies have the potential to do what we believe it will do in treating these diseases."

### How about the developments with QR-421a for Usher syndrome?

"Well, it's not as far as sepofarsen, but the collaboration with ProQR so far has been fantastic. They're transparent, forthcoming and I'm impressed with their level of professionalism. They really know how to bring something to the clinic with a high regard for safety. We're actually looking at additional projects to work on together."

### Do you feel like they mirror your high regard for patients?

"Definitely. They really go the extra mile to ensure safety. My personal yardstick is whether I would put my own children in a trial. If I can't say that, then I don't want to be involved. And with ProQR, the answer is 'absolutely."

*"ProQR really goes the extra mile to* **ENSURE SAFETY"**

### You seem to have a strong personal connection with the foundation's cause...

"I do – I have two actually. I have a relative with a rare inherited form of retinal degeneration, and the more common age-related macular degeneration runs in my family. I participate in a clinical study because of this, and I can tell you – some of those tests are not a lot of fun! But it means that I have an appreciation for the tests that patients are required to complete in order participate in our studies, and that motivates me to really think about when tests are necessary and why. On a higher level, we often don't realize how much we use vision – it's underappreciated. Blind people have to learn everything by heart, like the layout of their apartment or the way to the shop, and they rely on others to help them by putting stuff back in the same place every time. Can you imagine what happens if someone carelessly leaves the dishwasher door down? We organize 'dinners in the dark' as a fundraiser, and it's really powerful for donors to have to learn that the potatoes are at six o' clock on their plate, or to keep track of their glass of water."

### Do you engage patients outside of studies?

"Yes, and it's amazing how this has changed since the foundation started in 1971. In the beginning, we looked at blindness as needing one cure. But now we know there are hundreds of different reasons, mechanisms and varieties of retinal degeneration. Obviously a big part of this is genetics, so we provide programs for patients to test for known genes, but also to identify new mutations. We still find new ones every year."

### How do you see the future for blind people?

"I'm cautiously optimistic. We've been going at it for almost half a century, but the last five years the advances have been out of proportion, really great. It's also hard to be specific. Will we find therapies for everything? That's a tall order. Will we be able to slow the progress of diseases? No doubt. Even in the quest for the Holy Grail, which is regrowing the retina from stem cells, we are making progress – even though it has a way to go. In the end, it's our job as a foundation to go out of business." ■

## WHAT ARE IRDS?

Inherited retinal diseases are a collection of rare retinal degenerations or retinal dystrophies, in which a genetic mutation causes loss of function or death of the light sensitive (photoreceptor) cells in the retina. Most common IRDs include retinitis pigmentosa, Usher syndrome, Leber's congenital amaurosis and Stargardt's disease. They represent the most common cause of severe visual impairment or blindness in children and people of working age. It is estimated that IRDs affect more than 2 million people worldwide. To date, around 300 genes have been identified that can cause IRDs when mutated. For the vast majority of IRDs no therapy is currently available. ■



**JESSICA IBBITSON**, VICE PRESIDENT
OF CLINICAL AND DEVELOPMENT OPERATIONS

# BREAKING BARRIERS TO BETTER THERAPIES

New therapies are thoroughly tested in clinical studies. This is necessary to ensure they are safe and efficacious, but for a company like ProQR, which aims to treat small groups of patients with rare diseases, innovating within the system is essential to removing the obstacles on the way to caring for patients. As one of our new faces of 2018, Jessica Ibbitson is trying to rethink the way we do clinical studies.

Jessica joined ProQR at the beginning of 2018, after several positions in the pharma industry. Her last job before the transition to Leiden was at Vertex Pharmaceuticals, where she worked on rare diseases. What drew you to ProQR?

"I loved what I was doing, but when ProQR approached me I knew I couldn't pass up on their offer. I was attracted by the fact that it was a smaller company, working on rare diseases too and patient-focused in a way I've never seen before. I saw an opportunity to be disruptive in terms of how we approach clinical studies."



*"ProQR is* **PATIENT-FOCUSED** *in a way I've never seen before"*

How do you see that now, after almost a year? What are your goals?

"One way I'm trying to make ProQR different is in our relationship with the hospitals that run our studies. We aim to have not just a closer relationship with them but a partnership. Even though we work with clinical research organizations, we recognize that it adds more links to a chain so we've decided to take on tasks in order to reduce those links. By taking on more tasks ourselves, we can limit the administrative burden of the doctor, so that they can spend more time with their patients. But there is more to this. A direct relationship also means that information travels more freely, which means that it's much easier for us to understand the daily practice of care, and what the challenges and barriers are for hospitals, doctors and patients. To make sure that they have no hesitations about joining a study, we need to eliminate as many of these barriers as possible.

These barriers are not only about value and information. As a smaller biotech company, we have to think about efficiency as well – and often these goals go hand in hand, because a direct relationship with a doctor who has only one point of contact means that things move not only better, but quicker too."

Which barriers are you going to tackle next?

"Well, in 2019 we're starting to introduce more digital technologies into our clinical trials. This, too, is about eliminating barriers for participation in clinical research. For example, we are trying to stimulate doctors to record more patient information digitally, on our eSource platform. This overcomes the inefficiency of double data entry, making it faster, more accurate and less costly. But let's not forget that it also generates insight more quickly, because it will instantly tell everyone involved how a treatment is going. And since this also allows the doctor to spend more time with the patient, it creates more value too."

How is the reception of this technology among doctors and hospitals?

"They are excited. We are aware that the world of clinical practice is very risk-averse. They have to get used to new technology, and be sure that changing their ways doesn't affect the quality of their care. To guarantee this, we work side-by-side to explain our vision in a way that makes them comfortable. They really are our partners in this, so we have to take this journey together.

The other two ideas we are going to implement in the next year are more patient-centric. We are going to launch wearable and voice-assistant devices. They are two sides to the same coin, because both are ways to increase data, reduce cost and reduce the burden on the patient and the hospital. The wearable is a bracelet that tracks activity and sleep. This is very relevant for many patients with eye-related diseases, because when you're visually impaired your day/night rhythm can also suffer. Of course the bracelet measures these things in real time, so it gives us and the doctor much more data to work with, and may uncover effects of the therapy that we would have otherwise missed.

The voice system is software that you can install on your voice assistant that you can talk to and give commands, like the Alexa device. The potential it carries is different, but multi-faceted. For example,

*"One ideal I have is* **'SITELESS CLINICAL STUDIES'"**

it can take questionnaires from patients without the need for them to carry and store papers, which is quicker and relieves patient burden. It could also remind them to go to an appointment at the hospital or to take their medication, which helps compliance. And last but not least, talking is much easier for patients with eye-diseases than reading and writing. Both the wearable and the voice assistant have the potential to reduce the time needed for visits to the study hospital. This is significant for the patients that we work for; as some of them have to fly or cross borders to visit the specialist."

### What is your ideal future scenario?

"We already went from a company that was maybe more traditional in study design, to, in a very short time, becoming really technology and digitally focused in terms of how we execute studies. Looking ahead, the ultimate disruption for me would be to have broken all barriers. One ideal I have is 'siteless clinical studies.' The need for a physician or hospital will never go away completely, but what if we could give patients a box containing their medication, their wearable and other needs, and they would be fully empowered. Then patients from all over the world could participate in our studies." ■

## THE THRU MY EYES APP

One digital innovation that Jessica is especially excited about is the Thru My Eyes app. It's an app we developed that allows people to experience how patients with a certain eye-disease are perceiving the world. Jessica: "The app is a simple but clever idea based around one question: how does a patient actually see? Using sliders, you can simulate certain characteristics of a disease, such as tunnel vision or visual acuity (sharpness of vision) on what the phone's camera is seeing. We coupled it to medically relevant values, so it's possible to set it to a certain individual's diagnosis. This is a great tool for the patient's loved ones to really get an idea of what he or she is going through. We're eager to develop the app further, adding more disease simulations and functionalities." ■



*Download the app via www.thrumyeyes.app*

Thru My Eyes

# ANNUAL REPORT 2018

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# Message from the CEO

Dear fellow shareholders,

A first look at interim results in our Phase 1/2 clinical trial suggests that our lead product candidate, sepofarsen, improved vision in patients with Leber's congenital amaurosis 10, the leading genetic cause of blindness in childhood. This is very encouraging and shows that our choice to focus on developing RNA therapies for rare genetic eye diseases is the right one. Only a small percentage of the 300 known genetic eye diseases currently have a treatment and we feel the responsibility to change that. Therefore, we are rapidly advancing our pipeline to have five programs for genetic eye disease in clinical trials in the next two years including QR-421a for Usher syndrome, the leading cause of combined deafness and blindness and QR-1123 for autosomal dominant retinitis pigmentosa.

During our R&D Day we laid out 'ProQR's Vision 2023' that details our strategy for the next five years. In this vision we have set ourselves the goal to build ProQR out into a multi-product independent commercial company for inherited retinal diseases by the end of 2023. In this period we aim to have our first two products approved and independently commercialized in the Western world, have three or more programs in late stage development, and have at least seven programs in earlier stages of development. This is a set of very ambitious goals that we aim for on our path to making a major impact to a large number of people around the world.

But we also look beyond genetic eye diseases into other areas where our RNA repair technologies can make a difference for patients. We plan to advance several other preclinical programs in our broader rare disease pipeline of RNA therapies for patients in need.

Daniel A. de Boer

# Key Figures

| | 2018 | 2017 |
|---|---|---|
| **Result from continued operations (in € 1,000)** | | |
| Net revenue | -- | -- |
| Other income | 5,761 | 1,495 |
| Research and development costs | (29,514) | (31,153) |
| General and administrative costs | (12,540) | (10,840) |
| Operating result | (36,293) | (40,498) |
| Net result | (37,086) | (43,675) |
| | | |
| **Balance sheet information (in € 1,000)** | | |
| Non-current assets | 1,864 | 2,544 |
| Current assets | 108,367 | 50,559 |
| Total assets | 110,231 | 53,103 |
| Total equity | 92,685 | 39,325 |
| Non-current liabilities | 9,386 | 5,284 |
| Current liabilities | 8,160 | 8,494 |
| | | |
| **Cash flows (in € 1,000)** | | |
| Net cash used in operating activities | (28,493) | (34,951) |
| Net cash used in investing activities | (312) | (121) |
| Net cash generated by financing activities | 86,457 | 26,640 |
| | | |
| **Ratio's** | | |
| Current ratio | 13.3 | 6.0 |
| Solvency (%) | 84.1 | 74.1 |
| | | |
| **Figures per share** | | |
| Weighted average number of shares outstanding | 34,052,520 | 25,374,807 |
| Basic and diluted earnings per share (in € ) | (1.08) | (1.72) |
| Cash flow per share (in € ) | 1.69 | (0.33) |
| | | |
| **Employees** | | |
| Average number of staff for the period | 127.7 | 139.9 |

# Management Board

We have a two-tier board structure consisting of our Management Board (raad van bestuur) and a separate Supervisory Board (raad van commissarissen). The Management Board operates under the chairmanship of the Chief Executive Officer and shares responsibility for the deployment of ProQR's strategy and policies, and the achievement of its objectives and results.

Under Dutch Law, the Management Board has ultimate responsibility for the management and external reporting of the Company and is answerable to shareholders at the General Meeting of Shareholders. Pursuant to the two-tier corporate structure, the Management Board is accountable for its performance to a separate and independent Supervisory Board.

The following table sets out information with respect to our Management Board member, his respective age and his position at the Company as of the date of this annual report.

| Name | Gender | Date of Birth | Position | Date of Appointment | Term expires |
|---|---|---|---|---|---|
| Daniel de Boer | Male | April 12, 1983 | Chief Executive Officer | February 21, 2012 | 2022 |

The following sets forth biographical information regarding our Management Board members.

*Daniel de Boer* is our founding Chief Executive Officer since our incorporation in 2012. Daniel is a serial-entrepreneur and passionate advocate for rare disease patients. He assembled a group of successful biotech executives as co-founders and built a team of a 150 experienced scientists and drug developers, devoted to creating RNA therapies for patients in need. Under Daniel's leadership ProQR initiated clinical trials in multiple development programs for rare diseases, and raised over $ 300M in funding, including an IPO on Nasdaq. Daniel is responsible for the overall strategy and general business in the company. Before founding ProQR, Daniel was founder and Chief Executive Officer of RNA Systems, PC Basic and Running IT, companies he led through phases of growth, developing and launching several products in multiple European countries. Daniel was also a co-founder of Amylon Therapeutics, a company developing therapies for genetic brain diseases. In 2018 Daniel was named "Emerging Entrepreneur of the Year" by EY.

During 2018 *René Beukema* was our Chief Corporate Development Officer and General Counsel. Mr. Beukema joined us in September 2013 and is a seasoned in-house corporate lawyer in the Dutch biotechnology arena. Prior to joining us, Mr. Beukema served as General Counsel and Corporate Secretary of Crucell N.V. for twelve years, following his experience as a Senior Legal Counsel at GE Capital / TIP Europe and Legal Counsel at TNT Express Worldwide. Mr. Beukema was also a venture partner of Aescap Venture, a life sciences venture capital firm. Mr. Beukema is co-founder and advisor of Mytomorrows N.V., a Dutch life sciences company. He holds a post-doctoral degree in corporate law from the University of Nijmegen in co-operation with the Dutch Association of In-house Counsel (Nederlands Genootschap van Bedrijfsjuristen) and a Master's degree in Dutch law from the University of Amsterdam. Mr. Beukema left the Company January 1, 2019.

# Supervisory Board

The Supervisory Board supervises the policies of the Management Board and the general course of affairs of ProQR and advises the Management Board thereon. The Supervisory Board, in the two-tier corporate structure under Dutch law, is a separate and independent corporate body.

The following table sets forth information with respect to each of our Supervisory Board members and their respective dates of birth. The terms of office of all our Supervisory Board members expire according to a rotation schedule drawn up by our Supervisory Board.

Our Supervisory Board is currently composed of the following members, all of whom are independent under applicable NASDAQ standards and all of whom, with the exception of Mr. Dinko Valerio and Mr. Antoine Papiernik are independent under the Dutch Corporate Governance Code (DCGC):

| Name | Gender | Nationality | Date of Birth | Position | Date of Appointment | Term expires |
|---|---|---|---|---|---|---|
| Dinko Valerio | Male | NL | August 3, 1956 | Chairman | January 1, 2014 | 2020 |
| Alison Lawton | Female | US | September 26, 1961 | Member | September 17, 2014 | 2022 |
| Antoine Papiernik | Male | FR | July 21, 1966 | Member | January 1, 2014 | 2021 |
| James Shannon | Male | GB | June 5, 1956 | Member | June 21, 2016 | 2020 |
| Paul Baart | Male | NL | November 9, 1950 | Member | June 10, 2015 | 2019 |

The following sets forth biographical information regarding our Supervisory Board members.

*Dinko Valerio* is one of our founders and currently serves as the chairman of our Supervisory Board. Mr. Valerio has served on our supervisory board since January 2014. Mr. Valerio is a scientist and an experienced biotech entrepreneur with experience in both public and private companies as CEO and board member. Mr. Valerio is founder and former CEO of Crucell N.V., a Dutch biotech company, and founder and former general partner of Aescap Venture, a life sciences venture capital firm. In 1999, Mr. Valerio was one of the founders of Galapagos Genomics N.V., a spinout from Crucell N.V. which develops novel mode of action medicines. In 2017 Mr Valerio became a boardmember of Amylon Therapeutics B.V., a 80% owned affiliate of ProQR Therapeutics N.V. Adding to his corporate experience, Mr. Valerio is a professor in the field of gene therapy of the hematopoietic system at the University of Leiden. He received his Master of Science degree in Biology from the University of Amsterdam in 1982 and completed his Ph.D. in Molecular Genetics with Honors at the University of Leiden in 1986. Mr. Valerio also was a visiting scientific specialist at Genentech Inc., San Francisco in 1985 and a postdoctoral fellow at the Salk Institute, San Diego from 1986 to 1987. He is an author on more than 100 articles in peer-reviewed journals and an inventor on 11 patent-families.

*Alison Lawton* has served on our supervisory board since September 2014. Ms. Lawton is currently Chief Executive Officer, President and Director of Kaleido Biosciences where she was previously President and Chief Operating Officer since Dec 2017. Previously, Ms. Lawton was Chief Operating Officer at Aura Biosciences, Inc, from 2015 to 2017, Ms. Lawton served as Chief Operating Officer at OvaScience Inc., a life sciences company, from January 2013 to January 2014. In addition, from 2014 to 2017, Ms. Lawton served as a biotech consultant for various companies, including as Chief Operating Officer consultant at X4 Pharmaceuticals. Ms. Lawton worked at various positions of increasing responsibility at Genzyme Corporation, or Genzyme, and subsequently at Sanofi-Aventis, following its 2011 acquisition of Genzyme, each a global biopharmaceutical company. Ms. Lawton served as head of Genzyme Biosurgery, where she

was responsible for Genzyme's global orthopedics, surgical and cell therapy and regenerative medicine businesses. Prior to that, Ms. Lawton oversaw Global Market Access at Genzyme, which included Regulatory Affairs, Global Health Outcomes and Strategic Pricing, Global Public Policy, and Global Product Safety & Risk Management. Before joining Genzyme, Ms. Lawton worked for seven years in the United Kingdom at Parke-Davis, a pharmaceutical company. Ms. Lawton serves on the board of directors of Verastem, Inc., a public biopharmaceutical company. She also served on the board of directors of Cubist Pharmaceuticals for three years until its acquisition by Merck &Co., Inc. in 2015. She currently sits on the Scientific Advisory Board for the Massachusetts Life Science Center. She is past President and Chair of the Board of Regulatory Affairs Professional Society and past FDA Advisory Committee member for Cell and Gene Therapy Committee. She earned her BSc in Pharmacology, with honors, from King's College London.

*Antoine Papiernik* has served on our supervisory board since January 2014. Mr. Papiernik is managing partner at Sofinnova Partners, which he joined in 1997, and was appointed chairman in 2017. Mr. Papiernik has been an initial investor and active board member in public companies like Actelion, Addex, Auris Medical, Orexo, NovusPharma (then sold to CTI), Movetis (then sold to Shire), Mainstay, Pixium and Stentys, which went public respectively on the Zurich Stock Exchange, the NASDAQ Global Market, the Stockholm Stock Exchange, the Milan Nuovo Mercato, the Belgium Stock Exchange, the Dublin Stock Exchange and EuroNext Paris, in Cotherix (initially NASDAQ listed, then sold to Actelion), Core Valve (sold to Medtronic), Fovea (sold to Sanofi Aventis)m Ethical Oncology Science (EOS, sold to ClovisOncology) and Recor Medical (sold to Otsuka). Mr. Papiernik is also a board member of private companies MedDay Pharmaceuticals, MD Start, Shockwave Medical, Reflexion Medical, Gecko Biomedical, SafeHeal, Highlife and Rgenix. Mr. Papiernik has an MBA degree from the Wharton School of Business, University of Pennsylvania.

*James Shannon*, MD has served on our Supervisory Board since June 2016. Mr. Shannon has had an extensive career in drug development and pharma. From 2012 until his retirement in 2015, Mr. Shannon was Chief Medical Officer at GlaxoSmithKline. Prior to that he was Global Head of Pharma Development at Novartis and Senior Vice-President, Clinical Development at Sterling Winthrop Pharmaceuticals. He held board positions at companies including Biotie, Circassia, Crucell, Endocyte, MannKind and Cerimon Pharmaceuticals. In 2017 he joined the board of directors of Horizon Pharma. He received his undergraduate and postgraduate degrees at Queen's University of Belfast and is a Member of the Royal College of Physicians (UK). Mr. Shannon currently holds board positions at Mannkind Corp (USA), myTomonows (NL), Horizon Pharma (Ire) and Immodulon (UK).

*Paul Baart* has served on our supervisory board since June 2015. Mr. Baart made his career in public accounting in both the Netherlands and the USA. At PwC the Netherlands he served on the management board and the supervisory board. He was also a member of the global board of PwC International. He has served many large (listed) and international clients in various industries. He held professional qualifications both in the Netherlands and in the USA. He was chairman of Royal NIVRA, the Dutch Institute of Registered Accountants (now NBA), member of the Dutch Council on Annual Reporting (RJ) and supervisory board member of Nyenrode Business University. Present roles include outside member Enterprise Chamber Amsterdam Court of Appeal (Ondernemingskamer) and chairman Supervisory Board Grant Thornton the Netherlands. He studied business economics at the Vrije Universiteit in Amsterdam, where he also passed the Registeraccountants exam.

# Management Board Report

**The Company**
ProQR Therapeutics N.V., or "ProQR" or the "Company", is dedicated to changing lives through the creation of transformative RNA medicines for the treatment of severe genetic rare diseases (sometimes called orphan diseases) such as Leber's congenital amaurosis 10, Usher syndrome type 2 and autosomal dominant retinitis pigmentosa. Based on our unique proprietary RNA platform technologies, we are growing our pipeline with patients and loved ones in mind.

ProQR was founded in February 2012 by Daniel de Boer, Gerard Platenburg, the late Henri Termeer and Dinko Valerio. Mr. de Boer is a passionate and driven entrepreneur and an advocate for patients with severe genetic diseases. He has assembled an experienced team of successful biotech executives as co-founders, management team members and early investors. The team has extensive experience in the discovery and development of products in multiple therapeutic areas. As of December 31, 2018, we had raised € 251 million in gross proceeds from our public offerings of shares on the NASDAQ Global Market and private placements of equity securities. In addition, we have received grants, loans and other funding from patient organizations and government institutions supporting our programs, including from Foundation Fighting Blindness, Epidermolysis Bullosa Research Partnership, Epidermolysis Bullosa Medical Research and the Dutch government under the innovation credit program. ProQR headquarters are located in Leiden, the Netherlands.

Our legal name is ProQR Therapeutics N.V. and we were incorporated in the Netherlands, on February 21, 2012. We reorganized from a private company with limited liability to a public company with limited liability on September 23, 2014. Our company has its statutory seat in Leiden, the Netherlands. The address of its headquarters and registered office is Zernikedreef 9, 2333 CK Leiden, the Netherlands, telephone number +31 88 166 7000. The name and address of our agent for service in the United States is CT Corporation System, 111 Eighth Avenue, New York, NY 10011. We also rent offices in the United States in Cambridge, MA.

Since September 18, 2014, our ordinary shares have been listed on the NASDAQ Global Market under the ticker symbol PRQR.

**Operations**
We are an innovative biopharmaceutical company engaged in the discovery and development of RNA-based therapeutics for the treatment of severe genetic rare diseases. Utilizing our RNA platform, we are building a pipeline of therapeutics for patients in need. Our drug development programs are based on single-stranded RNA oligonucleotides that are chemically modified to enhance stability and cellular uptake, and intended to correct the underlying cause of the disease through repairing the genetic defect in the RNA. While all our compounds are RNA-based, a variety of mechanisms of actions may be used depending on the type of mutation causing the disease. We believe that this targeted approach offers several advantages compared to other therapeutic approaches in the treatment of the rare genetic diseases we target.

Our current pipeline consists of programs in ophthalmology and dermatology. In ophthalmology, we have a deep and broad pipeline with sepofarsen (formerly named QR-110) for Leber's congenital amaurosis 10, or LCA10 as our most advanced program. We are currently planning to start a potential pivotal Phase 2/3 clinical trial with sepofarsen during the first half of 2019 while completing a Phase 1/2 clinical trial that reported a rapid and sustained improvement in vision during an interim analysis. In dermatology, our most advanced program, QR-313, targets dystrophic epidermolysis bullosa, or DEB, a severe genetic blistering skin disease. We recently announced that post a planned interim analysis from our ongoing blinded Phase 1/2 clinical trial

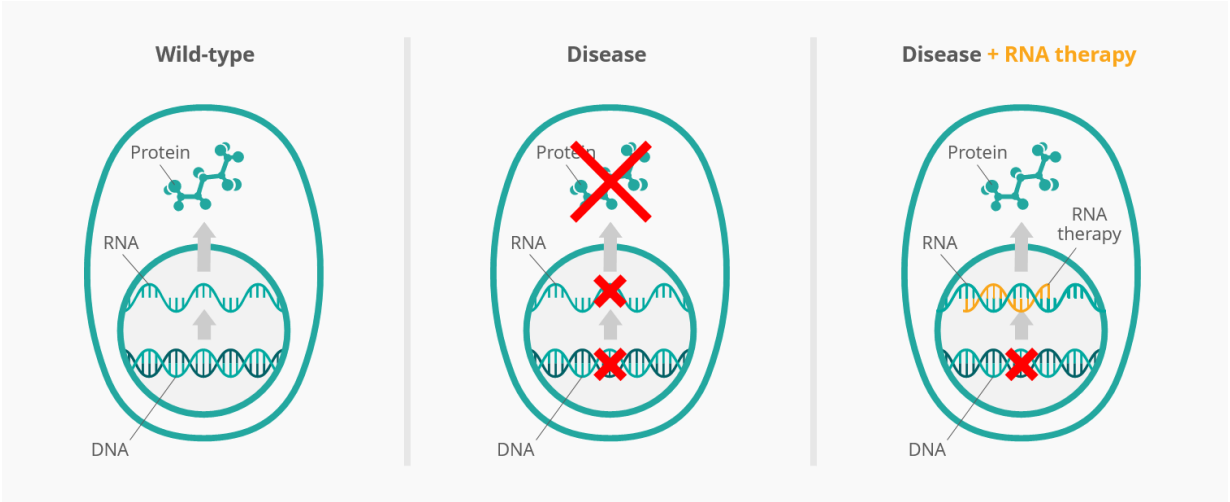
and a strategic review of our portfolio, further development of this program will be conducted by Wings Therapeutics.

Beyond our clinical portfolio, we have discovered and developed a novel proprietary RNA editing platform technology called Axiomer®. Axiomer's editing oligonucleotides, or EONs, are designed to recruit endogenous Adenosine Deaminases Acting on RNA, or ADAR, enzymes to make single nucleotide changes in the RNA in a highly specific and targeted manner at a desired location. We believe our Axiomer platform may be applicable to more than 20,000 disease-causing mutations.

We continue to assess our development and commercialization plans for our product candidates and intend to evaluate opportunities for beneficial collaborations or partnerships for these programs. In addition, using our discovery engine that is designed to generate a deep and broad pipeline of product candidates, we seek to enter into strategic partnerships for programs that we believe will benefit from such a partnership, and advance other selected programs independently to commercialization.

**Our RNA Repair Technologies**

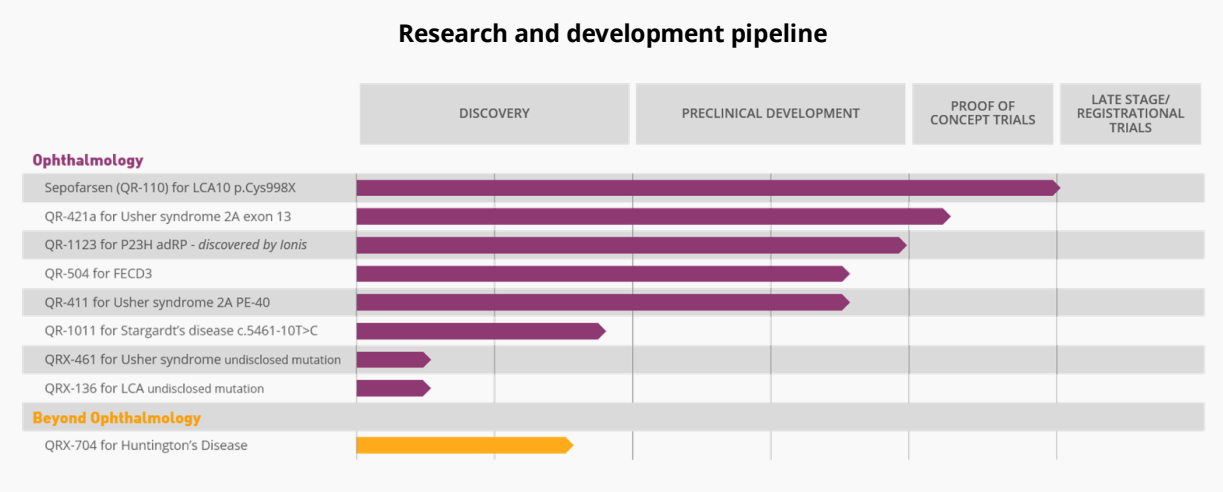
DNA contains genes that provide the instructions for the body to make all the functional building blocks of the cells, such as proteins. To get from DNA to protein, the cell first copies the information in the DNA into RNA during a process called transcription. The RNA then acts as the blueprint for making proteins during a process called translation. Genetic diseases are caused by mutations, or defects, in the DNA. These mutations are copied into the RNA blueprint, which means the resulting protein is also made incorrectly. The result is a missing, defective or toxic protein that prevents the cell from carrying out its normal function causing the disease.




We have gathered a toolbox of novel RNA repair technologies with which we believe we can use to target genetic diseases that are currently untreatable or have limited effective treatment options. Repairing RNA can take away the underlying genetic cause of the disease without having to make permanent changes to a patient's DNA. Our current molecules are all single-stranded RNA-based oligonucleotides that are chemically modified so that no vector or envelope is needed for delivery.

The toolbox of technologies range from splice correction in which we aim to restore normal messenger RNA and protein, exon skipping in which we aim to exclude the mutated part of the RNA and restore protein function to a gapmer technology that could prevent the formation of a toxic mutated protein. We believe our RNA repair approach has several advantages over DNA approaches such as gene therapy and gene editing.

These RNA repair approaches could allow us to develop novel RNA therapies for genetic diseases and make a meaningful impact on the lives of patients suffering from them.




***Sepofarsen for Leber's Congenital Amaurosis 10***

Leber's Congenital Amaurosis (LCA) is the most common genetic cause of blindness in childhood of which LCA10 is one of most severe forms. People with LCA10 typically become blind within the first few years of life and there are currently no approved therapies. The most common mutation is the p.Cys998X (also known as c.2991+1655A>G) in the *CEP290* gene. Although prevalence rates vary, based on our estimations, we believe this mutation occurs in approximately 2,000 patients in the Western world.

We are developing sepofarsen (formerly named QR-110) for patients who have LCA10 due to the p.Cys998X mutation. Sepofarsen aims to repair the underlying cause in the RNA by splice correction. This RNA splice correction is designed to result in the production of the normal, or wild type, CEP290 protein stopping or potentially reversing the disease. Sepofarsen is designed to be administered through intravitreal injections in the eye.

A Phase 1/2 clinical trial is ongoing in adults and children with LCA10 due to the p.Cys998X mutation. In September 2018, we reported an interim analysis confirmed clinical proof-of-concept as shown by a rapid and sustained improvement in vision in the majority of patients. In January 2019, we reached agreement with the U.S. Food and Drug Administration (FDA) on the design of a proposed Phase 2/3 clinical trial for sepofarsen. This planned Phase 2/3 clinical trial, named ILLUMINATE, is expected to start during the first half of 2019 and could serve as the sole registration trial for the program. Beyond sepofarsen, we have an additional discovery-stage program, QRX-136, for another mutation in *CEP290*.

Sepofarsen has been granted orphan drug designation by the FDA and European Commission and received fast track designation by the U.S. FDA

***QR-421a and QR-411 for Usher syndrome type 2***

Usher syndrome is the leading cause of combined hearing loss and blindness. To date, there are no therapies approved or product candidates in clinical development that treat the vision loss associated with the disease. Usher syndrome type 2 is one of the most common forms of Usher syndrome and is caused by mutations in the *USH2A* gene which encodes a protein called usherin.

We are developing QR-421a for *USH2A* exon 13 mutations and QR-411 for the *USH2A* PE40 mutation. In the Western world, approximately 16,000 patients have vision loss due to mutations in exon 13 of the *USH2A* gene and approximately 1,000 patients are affected by the PE40 mutation. Both product candidates are RNA

therapies intended to be administered by intravitreal injections and that aim to restore functional usherin protein in the eye to restore vision. Beyond QR-421a and QR-411 we have an additional discovery-stage program, QRX-461, for another mutation in *USH2A*.

Clinical development of QR-421a has begun and we plan to announce data from the ongoing Phase 1/2 safety and efficacy trial, named STELLAR, in mid-2019. QR-411 is currently in preclinical testing.

QR-421a and QR-411 have received orphan drug designation from the FDA and EMA. QR-421a was also granted fast track designation by the FDA.

***QR-1123 for autosomal dominant retinitis pigmentosa***
Autosomal-dominant retinitis pigmentosa (adRP) is characterized by progressive loss of vision. Symptoms typically start in early teenage years and include night blindness and reduction of the peripheral vision leading to tunnel vision. Eventually patients lose their central vision and become completely blind during adulthood. In the United States, the P23H mutation in the *RHO* gene is the most common mutation causing adRP and affects approximately 2,500 patients.

We are developing QR-1123 that was discovered by Ionis Pharmaceuticals and in-licensed by us in October 2018. QR-1123 is designed for the treatment of P23H adRP by suppressing the formation of the toxic mutant protein. By mutant-specific knockdown, QR-1123 selectively targets the mutant P23H RNA for destruction by RNase H1 cleavage without affecting the wild-type RNA. By reducing the mutant RNA, the resulting toxicity-induced loss of photoreceptors and subsequent loss of vision can potentially be stopped or reversed.

Currently, the QR-1123 program is undergoing the final preparation stages for IND submission. We plan to advance the QR-1123 program into a Phase 1/2 clinical trial during 2019.

***QR-313 for Dystrophic Epidermolysis Bullosa (DEB)***
Dystrophic epidermolysis bullosa (DEB) is a devastating skin disease that results in severe blistering and poorly healing wounds over the entire body, including mucosal membranes. Patients with the recessive form of DEB (RDEB) have a limited life expectancy and low quality of life. There is currently no treatment available for DEB besides intensive and costly palliative care. DEB is caused by mutations in the *COL7A1* gene which leads to an absence of functional collagen type VII (C7) protein which is essential for the formation of anchoring fibrils that link the outer layers of skin, the epidermis, to the dermis.

We are developing QR-313 for exon 73 mutations in the *COL7A1* gene. Approximately 2,000 DEB patients in the Western world have a mutation in this part of the gene. QR-313 is designed to be topically applied to a patient's wounds as a hydrogel and aims to restore functional C7 protein that is able to form anchoring fibrils to improve the strength of the skin. Beyond QR-313, we have a pipeline of discovery-stage programs for other mutations that cause DEB.

Subsequent to a planned interim analysis and strategic review, management has elected to transfer conduct and completion of the ongoing Phase 1/2 study to Wings Therapeutics. The ongoing Phase 1/2 trial in patients with DEB due to a mutation in exon 73 will remain blinded and continues to enroll patients. ProQR will work closely with Wings Therapeutics and EBRP to support its efforts to advance QR-313 for patients with DEB.

QR-313 has received orphan drug designation from the FDA and EMA.

***Eluforsen for Cystic Fibrosis (CF)***
Cystic fibrosis (CF) causes viscous mucus to accumulate in vital organs disrupting several processes in the body. Pancreatic enzymes are blocked from entering the intestines and the thick layer of mucus in the lungs

is a great environment for destructive bacteria. The thick mucus makes it hard to clear the lungs from these bacteria and results in regular infections and inflammation. This process injures the lungs and leads to frequent hospitalizations and lung failure.

We are developing eluforsen for the most common mutation causing CF, the F508del mutation in the *CFTR* gene, affecting approximately 85% of all CF patients. Two global clinical trials for eluforsen in people with CF have been completed. Study 001, a Phase 1b safety and tolerability clinical trial in 70 CF patients and Study 002, a proof of concept clinical trial in 18 CF patients. In both clinical trials eluforsen was observed to be safe and well-tolerated and both trials showed encouraging signals that eluforsen has the potential to be a meaningful therapy for people with CF that have two copies of the F508del mutation (homozygotes).

Eluforsen has received orphan drug designation from the FDA and EMA. Eluforsen was also granted fast track designation by the FDA.

***Axiomer® RNA Editing Technology***

The Axiomer® platform is a novel, proprietary RNA editing technology invented at ProQR. The technology is based on editing oligonucleotides, or EONs, designed to recruit ADAR enzymes (Adenosine Deaminases Acting on RNA) to make single nucleotide changes in the RNA in a highly specific and targeted manner at a desired location. The approach, for which ProQR is pursuing patent protection, allows the recruitment of endogenous ADARs by using EONs as the sole drug modality, doing away with the need for overexpression of (artificial) ADAR proteins, guide RNAs or other large, complex components.

Recruitment of endogenous RNA-editing enzymes by EONs represents a significant therapeutic opportunity for a new type of drugs that can treat genetic diseases by reversing the underlying mutations. ADARs are present in most human cells and naturally make adenosine-to-inosine (A-to-I) changes in RNA. Since an inosine is interpreted by the cell as a guanosine, an EON-mediated, targeted editing reaction has the potential to effectively modify any chosen adenosine (A) in any RNA to a guanosine (G). This can either restore the original sequence, or bring about an intended *de novo* A to G change, in order to treat genetic disease. Current estimations point to over 20,000 G to A mutations in the human population that cause disease.

*In vitro* and *in vivo* work indicates that the EONs are generally applicable for the correction of mRNA G-to-A mutations. Together with the leading academic experts in RNA editing, we continue to advance our Axiomer RNA Editing technology to develop therapies for genetic diseases.

***Early stage pipeline***

Beyond the programs mentioned above we have additional early stage programs in our pipeline targeting genetic diseases with profound unmet medical need.

*QR-504 for Fuchs endothelial corneal dystrophy*

Fuchs' endothelial corneal dystrophy 3 (FECD3) is a common, autosomal dominant, degenerative condition of the eye. With age the endothelial cells are lost, ultimately leading to progressive corneal clouding, reduced vision and painful epithelial bullae. There are currently no treatment options other than corneal (endothelium) transplantation for patients with advanced disease. The availability of donors, risk of rejection, and the inherent risk of an invasive procedure are some of the limitations of this procedure. FECD3 is caused by a trinucleotide CTG repeat expansion in the *TCF4* gene. It is estimated that FECD affects more than 4% of individuals over the age 40 in the U.S., and similar prevalence is noted for other global regions. The mutated TCF4 mRNAs accumulate as nuclear RNA foci and globally disrupt mRNA splicing in the corneal endothelial cells. QR-504 targets the mutated mRNA with the aim to reduce the accumulation and splicing disruption. QR-504 is currently in discovery stage and we intend to commence IND-enabling studies.

*QR-1011 for Stargardt's disease*

Stargardt's disease is the most common inherited macular dystrophy causing progressive loss of central vision. Most patients with Stargardt's disease will progress to legal blindness or worse as they age. Currently, there is no treatment available. It is associated with mutations in the *ABCA4* gene resulting in the loss of photoreceptor cells in the retina. The c.5461-10T>C mutation affects about 7,000 patients in the Western world and leads to aberrant splicing of ABCA4 mRNA. QR-1011 aims to restore normal splicing leading to the production of wild type mRNA and protein thereby stopping or potentially reversing the disease. QR-1011 is currently in the advanced lead optimization phase.

*QRX-704 for Huntington's Disease*

Huntington's disease (HD) is an inherited progressive neurodegenerative disease, and one of the most common genetic disorders. Symptoms include involuntary movements, incoordination, impaired speech, cognitive decline and depression. Patients with HD have a shortened life expectancy and there is currently no disease-modifying treatment available. The disease is caused by an expanded repeat of CAG nucleotides in the HTT gene, resulting in a mutated huntingtin protein that is cleaved into toxic fragments, which accumulate in nerve cells. QRX-704 is designed to modify HTT mRNA to prevent the formation of the toxic fragments, while the huntingtin protein remains functional. QRX-704 is currently in discovery stage.

**Our Strategy**

We are dedicated to improving the lives of patients and their loved ones through the development of RNA therapies for severe genetic rare diseases. We believe the strategy as outlined below enables us to build a sustainable independent business which creates value for all stakeholders involved. Key elements of our strategy include:

- ***Develop drugs for patients in need.*** Through our patient-centric approach we work to develop best-in-class therapies and to advance the understanding of conditions that we target. As RNA therapies have become an established modality, we are translating new applications in a pipeline of products for patients suffering from rare diseases.
- ***Rapidly advance our ophthalmology platform.*** The initial results of sepofarsen in restoring vision as observed during the interim analysis of the Phase 1/2 trial have built confidence in the potential opportunity for RNA therapies in treating genetic eye diseases. Therefore, we plan to rapidly advance our programs in ophthalmology for a range of genetic eye diseases for which there are no or limited treatment options. As part of our five-year plan known as our "ProQR Vision 2023 strategy", by 2023, we aim to obtain marketing approvals for the first two products in our ophthalmology pipeline, and build a deep pipeline of ten or more programs beyond those two products, of which we expect three to be in late stage development.
- ***Commercialize portfolio of ophthalmic medicines independently.*** We plan to commercialize our portfolio of medicines for inherited retinal diseases (IRDs) independently in North America and Europe, and seek partners for other geographic areas. While building the commercial infrastructure for an expected commercial launch of sepofarsen in 2021, we expect this same infrastructure to serve patients with other IRDs like Usher syndrome or Stargardt's disease as IRD patients are typically seen by one of the 30 IRD hub centers.
- ***Leverage our pipeline through strategic consideration of out-licensing, spinouts or collaborative partnerships.*** We plan to continue to advance the programs and technologies in our discovery pipeline beyond ophthalmology and selectively engage with partners for development and commercialization of programs and products that we do not intend to independently develop.
- ***Expand our Axiomer RNA-editing platform into select therapeutic areas.*** Our novel and proprietary RNA editing platform technology, Axiomer, is a new way to use oligonucleotides to edit single nucleotides in the RNA. We believe our Axiomer technology may be applicable to more than 20,000 disease-causing mutations. In 2019 and beyond, we plan to build out Axiomer in select therapeutic areas and continue to

validate and create value for the platform through pursuing licensing, partnering and other strategic relationships.

**Patient Centric Approach**

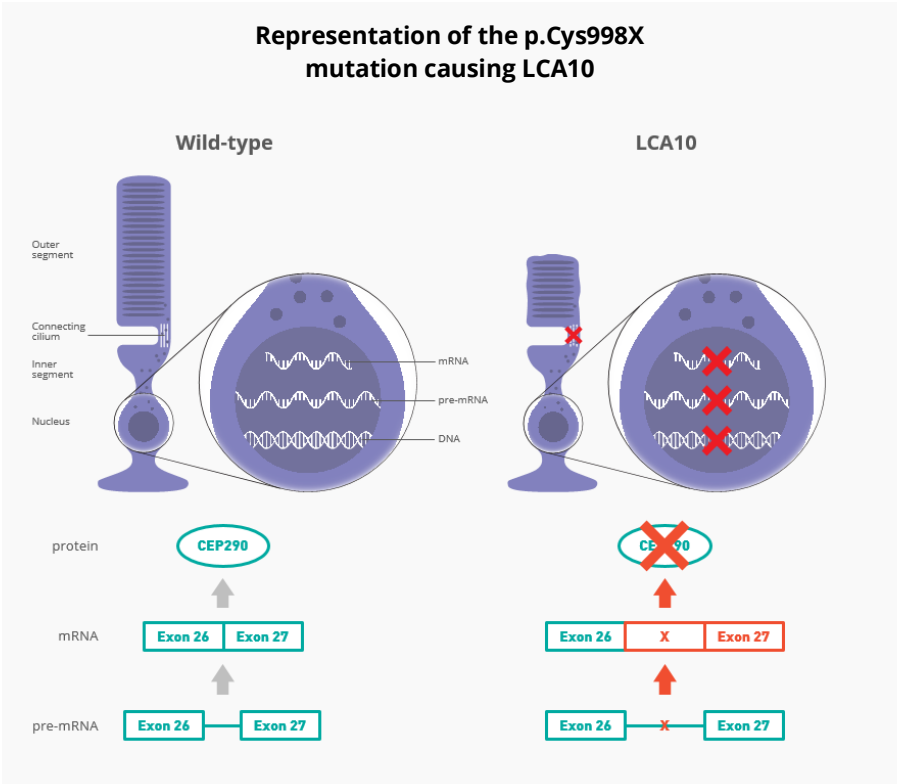
ProQR aims to develop best-in-class therapies as well as to improve patient care through awareness, education, and advancing the understanding of conditions that we target. In order to achieve this goal, ProQR strives to integrate the patient voice into our decision-making throughout the drug development process as we believe that a patient-centric strategy is crucial to our success. Therefore, our Patient and Medical Community Engagement (PMCE) team actively collaborates with and listens to the communities we serve to ensure that the patient voice is represented internally.

**Sepofarsen for Leber's Congenital Amaurosis 10 (LCA10)**

***LCA background***

Leber's Congenital Amaurosis (LCA) is the most common genetic cause of blindness in childhood. The p.Cys998X mutation (also known as c.2991+1655A>G) in the *CEP290* (Centrosomal protein of 290 kDa) gene is the most prevalent mutation which generally accounts for the most severe disease phenotype (LCA10). This mutation leads to significant decrease in CEP290 protein within the photoreceptor cells in the retina. Patients affected by this mutation typically lose sight in the first years of life. Clinical features of LCA10 include loss of vision, involuntary eye movement or nystagmus, abnormalities of pupil reactions and no detectable photoreceptor electrical signals on electroretinography (ERG).

**Representation of the p.Cys998X mutation causing LCA10**




***LCA genetics***

More than 20 genes have been associated with the genetic defect that causes LCA. The most common mutation is the p.Cys998X in the *CEP290* gene causing LCA10. The p.Cys998X mutation is a single nucleotide substitution in the *CEP290* gene that creates a new splice site, also called a cryptic splice site, between exon 26 and 27. During the splicing of the pre-mRNA this causes a part of the intron, or pseudoexon, to be included in the mRNA. The pseudoexon contains a premature stop codon thus the mRNA is not translated into the full length CEP290 protein. CEP290 protein is involved in the formation and stability of the connecting cilium in photoreceptor cells, which facilitates the transport of proteins from the inner segment to the outer segment of the cell. When CEP290 is absent, there is a disturbance in normal protein transport to the outer segments of the photoreceptor cell which provokes the shortening of the outer segment and its inability to perform its light transducing function.

***LCA Prevalence and Diagnosis***

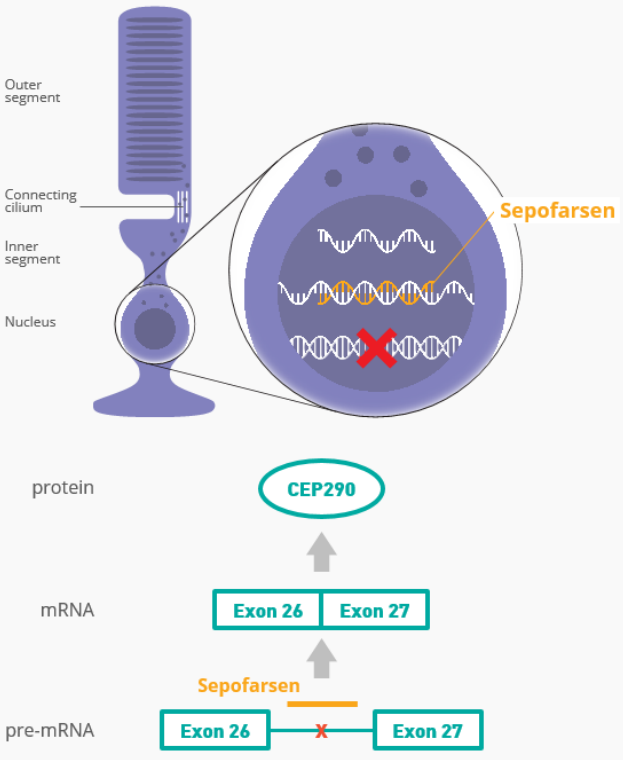
LCA affects about 15,000 patients in the Western world. Although diagnosis rates vary, our estimations indicate the most common p.Cys998X mutation occurs in approximately 2,000 patients in the Western world.

Patients are initially diagnosed through the presence of clinical symptoms. Nystagmus, rapid involuntary movements of the eyes, tends to be the first symptom visible as well as oculo-digital signs comprising eye poking, pressing, and rubbing. Vision impairment or blindness becomes obvious as age increases. After an ophthalmological examination, LCA is diagnosed. A genetic screening including all known mutations causing LCA is performed to confirm the diagnosis and determine the type of LCA in order to give the patient the most accurate prognosis possible (approximately 30% of all patients carry a mutation that has not been identified to date).

***Approaches for the Treatment of LCA10***

There are currently no disease modifying treatments approved for patients with p.Cys998X associated LCA10 and disease management is currently supportive in nature. The eye is highly suitable for oligonucleotide therapies as it is a contained organ with physical cellular barriers. These natural barriers strongly limits the free entry and exit of cells and larger molecules in and out of the eye, therefore limiting the systemic exposure of locally administered therapies.

**Sepofarsen for LCA10, splice correction for p.Cys998X *CEP290* mRNA**




Sepofarsen binds to pre-mRNA and silences the cryptic splice site leading to production of normal mRNA

***Sepofarsen for the treatment of LCA10***

Sepofarsen (formerly named QR-110) is designed to treat LCA10 by splice correction. By binding to the pre-mRNA sepofarsen aims to silence the cryptic splice site caused by the p.Cys998X mutation. The splicing machinery can thus process the pre-mRNA correctly resulting in normal mRNA and we expect the production of full-length functional wild type CEP290 protein. Sepofarsen is designed to be administered by intravitreal injection.

Sepofarsen has received orphan drug designation from the U.S. FDA and European Commission. Sepofarsen was also granted fast track designation by the U.S. FDA.

***Clinical Development for Sepofarsen***

The activity seen in our preclinical models of LCA10 provided strong support for the clinical development and therapeutic potential of sepofarsen. The clinical development of sepofarsen began in the second half of 2017 with a Phase 1/2 open-label, multiple dose, dose escalation study to evaluate the safety and tolerability of sepofarsen, study PQ-110-001. This trial is currently ongoing (enrollment complete) and includes five children (age 8 - 17 years) and six adults (≥ 18 years) who have LCA10 due to one or two copies of the p.Cys998X mutation in the *CEP290* gene. Participants were to receive up to four intravitreal injections of sepofarsen into one eye; every three months. Based on updated data suggesting a longer half-life of sepofarsen in the retina, dosing of patients has been adjusted to once every six months

after receiving their first 2 injections 3 months apart. The study is being conducted in three centers with significant expertise in genetic retinal disease in the U.S. and Europe.

The primary objectives of the trial are safety and tolerability. Secondary objectives include the pharmacokinetics and restoration/improvement of visual function and retinal structure through ophthalmic endpoints such as best-corrected visual acuity (BCVA), full-field stimulus testing (FST), optical coherence tomography (OCT), pupillary light reflex (PLR), mobility course and oculomotor instability (OCI). Reports of substantial improvement in vision in one subject led to the decision to perform an interim analysis of data collected as of August 16, 2018.

*Safety data:*
At the time of the interim analysis (August 16, 2018), treatment-emergent adverse events (TEAEs) reported were mostly mild and there had been no signs of intraocular inflammation. Mild local reactions related to the injection procedure such as conjunctival hemorrhage were reported; such events are typical with intravitreal injection. To support regulatory discussions (in December 2018) related to advancing the program into a potential registrational trial, a further safety follow-up was conducted after the interim analysis, in which, adverse events observed after longer duration of treatment included mild cystoid macular edema and lens opacities. The cystoid macular edema was observed in two patients in the highest dose tested and was responsive to standard of care treatment. There were six participants with lens opacities, of which three went on to have corrective lens replacement. These events were considered likely related to study medication and are consistent with those seen for other ophthalmic and intravitreal oligonucleotide therapies. Dosing adjustments (dose and dosing interval) were made. There have been no discontinuations from the study.

*Efficacy data:*
The interim analysis of efficacy data from PQ-110-001 confirmed clinical proof-of-concept as shown by improvement in BCVA and supported by improvement in performance on the mobility course and reduced involuntary eye movement (nystagmus). Mechanistic proof-of-concept was confirmed by improvement in FST. Importantly, the four endpoints analyzed showed concordant improvement (Table 1). In approximately 60% of subjects, multiple independent measures of visual function were improved in the treated eye, but not in the contralateral eye.

**Table 1 Summary of Efficacy Endpoints Assessed for the Interim Analysis (Data Cutoff 16 August 2018)**

| Endpoint | Units | Direction Showing Improvement | Responder Threshold | Change from Baseline at Month 3 Mean (SEM) | |
|---|---|---|---|---|---|
| | | | | Treated | Untreated |
| **Overall** | | | | | |
| Best corrected visual acuity (ETDRS/BRVT) (n=8) | LogMAR | ↓ = improved | ≥ -0.3 | -0.67 (0.32) | 0.02 (0.05) |
| Full field stimulus red (FST red) (n=7) | $cd/m^2$ | ↓ = improved | | -0.74 (0.35) | -0.23 (0.18) |
| Full field stimulus blue (FST blue) (n=7) | $cd/m^2$ | ↓ = improved | | -0.91 (0.38) | -0.02 (0.11) |
| Mobility course (n=7) | Level | ↑ = improved | ≥ 2 | 2.57 (1.19) | 1.36 (1.04) |
| OCI (nystagmus tracking) (n=7) | $Log_{10}mm$ | ↓ = improved | | -0.14 (0.08) | -0.04 (0.06) |

Abbreviations: BRVT=Berkeley Rudimentary Vision Test; $cd/m^2$=logarithm of candelas/square meter; ETDRS=Early Treatment Diabetic Retinopathy Study; LogMAR=Logarithm of the Minimum Angle of Resolution; OCI = Oculomotor Instability

Measurements of best corrected visual acuity (BCVA), functional vision (mobility), and nystagmus confirm vision improvement in these subjects. In addition, clear improvement in FST was seen at both red and blue wavelengths in the treated eye only.

BCVA is an accepted registration endpoint for treatments of retinal diseases, with a generally-accepted threshold for clinically meaningful improvement of -0.3 LogMAR (15 letters on an eye chart). At Month 3, this threshold was exceeded in treated, but not untreated eyes, in the overall population, both in adult and pediatric subjects.

Performance on a mobility course was also improved, and nystagmus was reduced. Concordant improvement in the mechanistic and functional outcome measures confirm that these observations are due to on-target benefits of sepofarsen. Results from the individual endpoints are discussed in more detail below.

***Best Corrected Visual Acuity (BCVA)***
To assess BCVA, either the ETDRS eye charts or BRVT eye charts (for subjects with more severe visual impairment) were used. ETDRS is useful up to LogMAR 1.6, and BVRT extends the range to LogMAR 4.0, or mere light perception.

Data from the three-month assessment of BCVA are shown for the available eight subjects in Figure 1. The dark and light green bars on the left represent mean (SEM) and median change from baseline, respectively, for the treated eye, and the gray bars (undetectable) on the right represent mean (SEM) and median change from baseline for the contralateral eye. Red triangles for the median bars represent individual subject values. The dotted horizontal line represents the clinically meaningful level of -0.3 LogMAR.

In the treated eye, both mean and median change from baseline were above the clinically meaningful threshold, while the contralateral eye showed no meaningful improvement. As can be seen in Figure 1, clinically meaningful improvement was seen in the treated eyes of 5 of the 8 subjects at Month 3, but no subject showed clinically meaningful improvement in the contralateral eye. Importantly, some subjects who were only able to perceive hand movement were able to read larger letters on the ETDRS eye chart at three-month.

Although the study was not powered to show statistical significance, comparison of the mean change from baseline in treated eyes to contralateral eyes at three-month was significant (p=0.011; Wilcoxon's rank-sum test).

**Figure 1 Mean (SEM) and Median Change from Baseline in BCVA at Month 3 (Interim Analysis)**

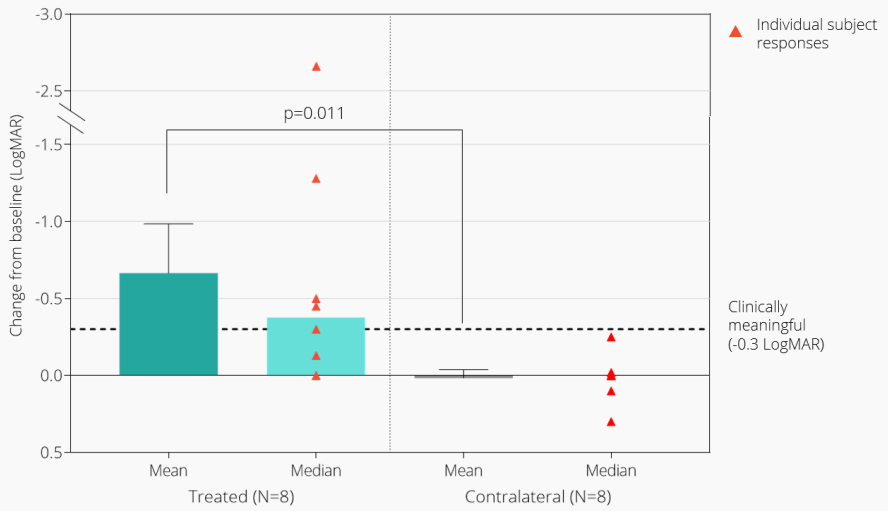



**Figure 2 Mean Change from Baseline in BCVA through Month 6 (Interim Analysis)**

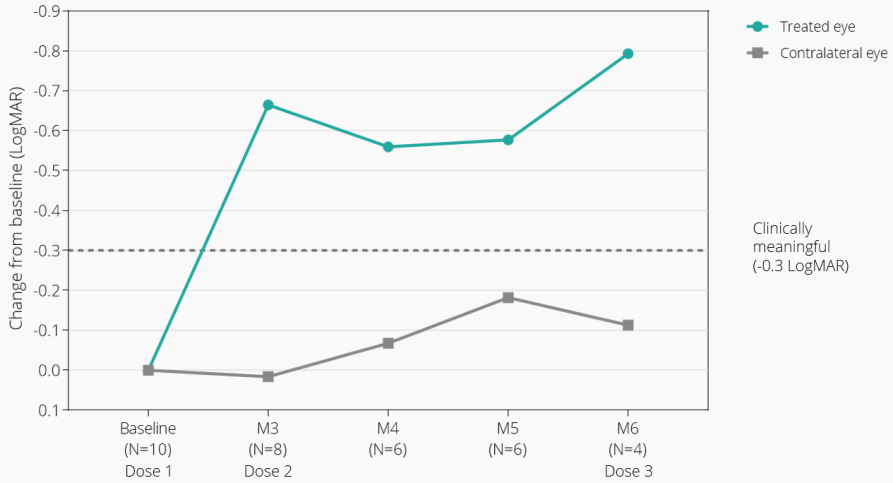



*Figure 2 shows mean changes over time for all available BCVA measurements for the treated eye (green line) and contralateral eye (gray line). The mean for the treated eye increased to a clinically meaningful extent after the loading dose, and remained stable thereafter. Clinically meaningful improvements were observed for the treated eye but not for the contralateral eye. This figure shows the three-month data for all eight subjects but also includes the six-month data for the four patients who had reached six-months at the time of the assessment.*

*Full-Field Stimulus Test (FST):*

The FST is a sensitive mechanistic outcome measure. This test is similar to a hearing test, but instead of subjects pushing a button when they first hear a progressively louder tone, in FST they push a button when they detect a progressively brighter red or blue light flashed across the entire retina. As FST is a very sensitive test, it was hypothesized that improvement in FST would be the earliest and most sensitive indication that sepofarsen was engaging its target.

Figure 3 shows the three-month mean (SEM) change from baseline in ability to see both blue and red wavelengths. The dark bars represent the treated eye and the lighter bars represent the contralateral eye. Improvement was observed in the treated, but not the contralateral eye for both wavelengths. Figure 4 shows the stability of the response over time using all available data. Improvement in the treated eye was observed to be well maintained. This figure shows the three-month data for seven subjects but also includes the six-month data for the four patients who had reached six months at the time of the assessment.

**Figure 3 Mean (SEM) Change from Baseline in Full-field Stimulus Test at Month 3 (Interim Analysis)**

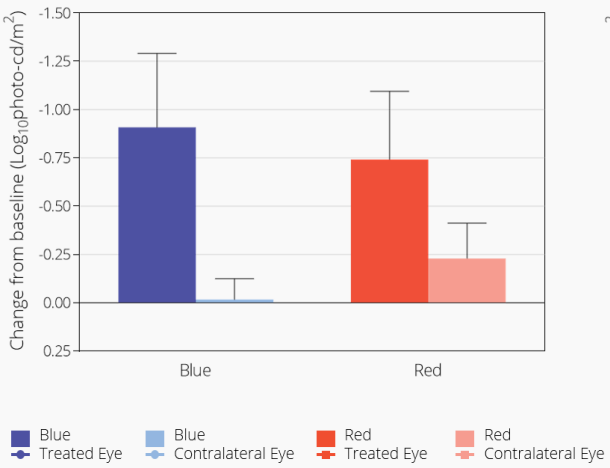
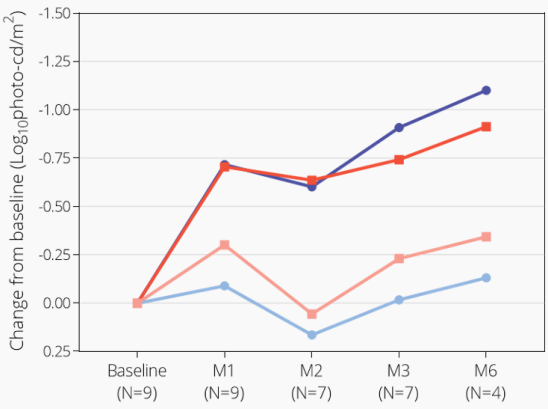



**Figure 4 Mean Change from Baseline in Full-field Stimulus Test through Month 6 (Interim Analysis)**




*Mobility Course*

A mobility course suitable for patients with LCA10 was developed to quantify improvements in functional vision. The tool involves different layouts of increasing complexity, using multiple light levels. In total, the series of courses produces 19 levels, with level 1 being the ability to navigate a short, straight course with a single brightly-backlit obstacle; the other end of the spectrum at level 19 is the ability to navigate a very dimly-lit complex course with multiple obstacles. Improvement is measured by the number of levels a patient is able to navigate.

Figure 5 shows the three-month mean (SEM) change from baseline in number of levels subjects are able to navigate. The green bar represents the treated eye and the gray bar represents the contralateral eye. Red triangles represent individual subject data points. Figure 6 shows the stability of the response over time using all available data. The green line represents the treated eye and the gray line represents the contralateral eye. The dotted horizontal line represents the anticipated clinically meaningful threshold for improvement of two levels, or approximately a ten-fold reduction in light required for the subject to successfully navigate the mobility course.

Clinically meaningful improvement was seen in the treated eye at three-months. Clinically meaningful improvement was also seen in the contralateral eye in some patients at three months. However, the group mean for the contralateral eye did not reach the level of being clinically meaningful. Also, this improvement in the contralateral eye appears to be transient, as shown in Figure 6.

Results from the mobility assessment support the functional significance of the best-corrected visual acuity improvement.

**Figure 5 Mean (SEM) Change from Baseline in Mobility Course Results at Month 3 (Interim Analysis)**

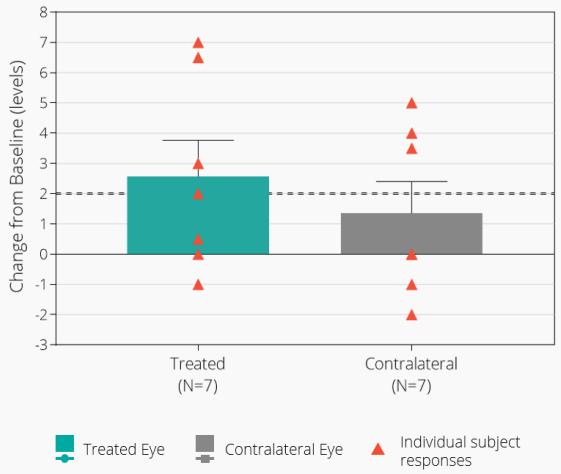
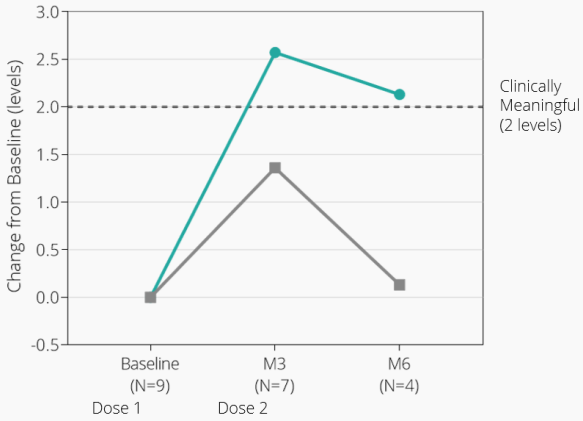



**Figure 6 Mean Change from Baseline in Mobility Course Results through Month 6 (Interim Analysis)**




*Oculomotor instability (OCI)*

Oculomotor Instability (OCI) (measurement of nystagmus) was also assessed for the interim analysis. Nystagmus is involuntary eye movements due to the inability to fixate. Oculomotor Instability quantifies nystagmus using laser tracking measurement of eye movement.

Figure 7 shows the three-month mean (SEM) change from baseline in level of nystagmus. The green bar represents the treated eye and the gray bar represents the contralateral eye. Red triangles represent individual subject data points. Figure 8 shows the stability of the response over time using all available data. The green line represents the treated eye and the gray line represents the contralateral eye. This figure shows the three-month data for seven subjects but also includes the six-month data for the four patients who had reached six months at the time of the assessment.

Nystagmus was observed to be improved in the treated eye at three months, compared to both baseline and the contralateral eye. This improvement was also noted by study investigators during their initial clinical assessment prior to OCI testing. As can be seen in the right panel, improvement in OCI was maintained in the treated eye over time, and potentially increased.

**Figure 7 Mean (SEM) Change from Baseline in Oculomotor Instability at Month 3 (Interim Analysis)**

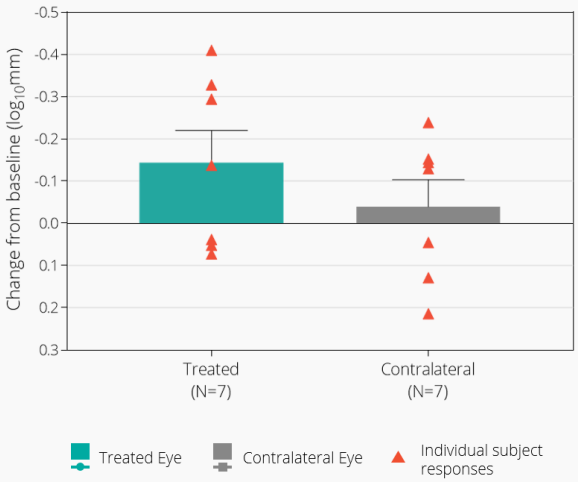
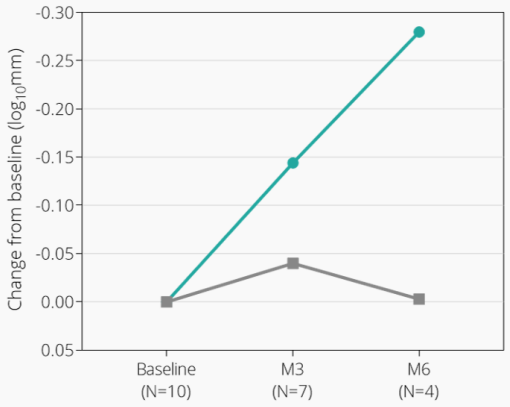



**Figure 8 Mean Change from Baseline in Oculomotor Instability through Month 6 (Interim Analysis)**



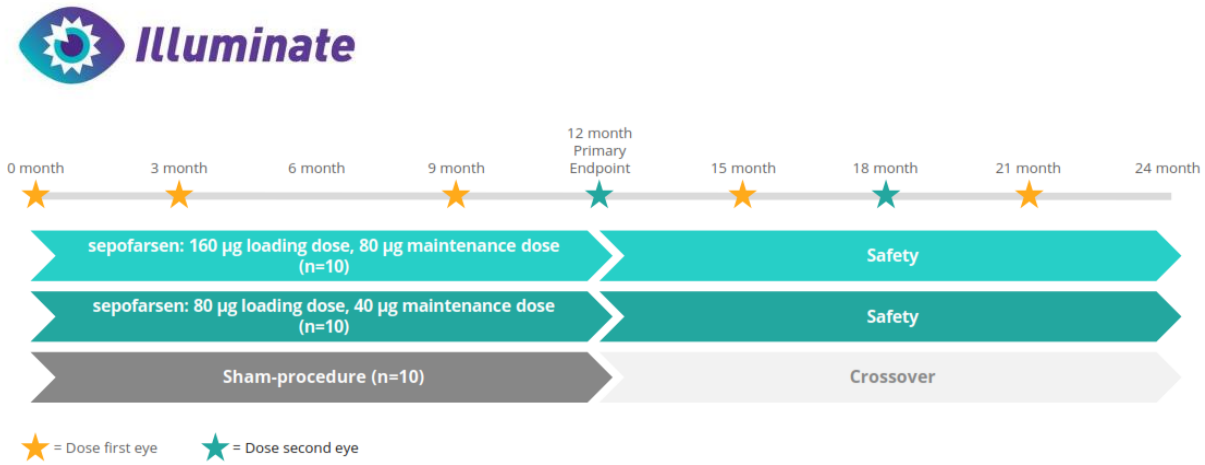

*Conclusions from Study PQ-110-001 (Interim Analysis)*

Available data from the interim analysis of PQ-110-001 support the clinical proof-of-concept of sepofarsen as shown by improvement in BCVA and supported by improvement in performance on the mobility course and reduced involuntary eye movement (nystagmus). Mechanistic proof-of-concept was supported by improvement in FST. Importantly, the four endpoints analyzed showed concordant improvement. In approximately 60% of subjects, multiple independent measures of visual function were improved in the treated eye, but not in the contralateral eye. Treatment-emergent adverse events reported beyond the interim analysis were mostly mild except for three lens opacity events that were reported as moderate or severe. We intend to conduct further testing of the long-term safety and efficacy of sepofarsen, as well as initiation of trials to explore dose response in a controlled manner.

*Next steps in clinical development of sepofarsen*

Study PQ-110-002 is an extension study to continue to provide treatment to subjects completing study PQ-110-001 for which the benefit/risk is positive. Study PQ-110-002 will allow for additional assessment of long-term safety, tolerability and (systemic) exposure of sepofarsen, as well as efficacy assessments, including sustained efficacy. Treatment of the contralateral eye may also be initiated.

In addition, the ILLUMINATE study (PQ-110-003) will also be initiated. This study is a double-masked, randomized, controlled, multiple-dose study to evaluate the efficacy, safety, tolerability and systemic exposure of sepofarsen administered via intravitreal injection in subjects with LCA due to the CEP290 p.Cys998X mutation. ILLUMINATE will include two active dose levels and a sham control group. Efficacy assessments, including BCVA, mobility course score, retinal imaging, functional assessments of vision, patient-reported outcome (PRO) measures, as well as safety assessments will be performed at selected study visits. The primary endpoint will be assessed at 12 months of treatment, but all efficacy and safety assessments will continue to be followed during the 24-month treatment period. Treatment of the contralateral eye may also be initiated.




Beyond sepofarsen we have an additional discovery-stage program, QRX-136, for another mutation in *CEP290*.

***Preclinical evidence for sepofarsen***

We have conducted *in vitro* and *in vivo* preclinical studies that support the clinical development of sepofarsen.

*Sepofarsen assessment in patient fibroblasts*

Since sepofarsen targets the splicing process, the most direct measurable outcome of activity is the profiling and quantification of *CEP290* transcripts (wild-type and mutant) and protein before and after treatment. In preclinical studies, sepofarsen demonstrated restoration of *CEP290* wild-type (correctly spliced) mRNA and protein in cultured fibroblast cells of LCA10 patients homozygous and compound heterozygous for the p.Cys998X mutation.

*Sepofarsen activity in optic cup model*

Optic cups are a retinal organoid model derived from fibroblasts of a LCA10 patient harvested through skin biopsies. The cells are reprogrammed into induced pluripotent stem cells, or iPSC, and later differentiated into retinal pigmented epithelium cells and neural retinal cells, also known as three-dimensional optic cups.

The clinical and molecular relevance of the optic cup model, coupled with the absence of an animal model, makes the optic cup the best model in which to simulate the mechanisms of LCA10 and effectively test the potential of sepofarsen.

LCA10 patient derived optic cups were exposed to sepofarsen. First, we observed from the results that sepofarsen is able to enter the cells without use of any transfection agents. Second, sepofarsen elicited a dose-dependent restoration of *CEP290* wild type mRNA expression. And third, increased *CEP290* mRNA expression was also associated with an increase in functional measures such as percentage of ciliated cells and the length of the cilia.

*Retinal Distribution of sepofarsen*

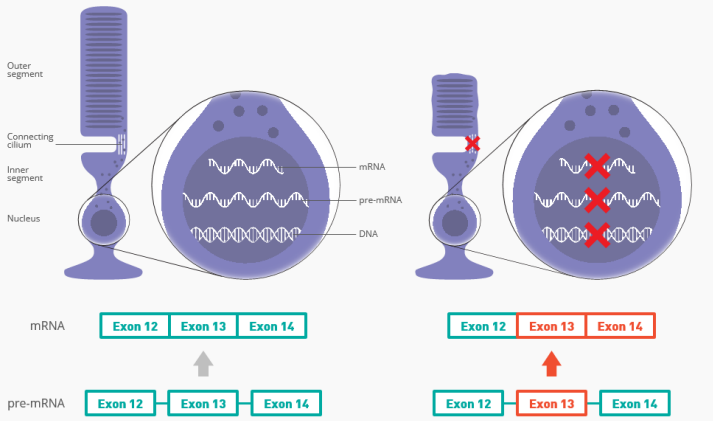
Using labelled sepofarsen administered via intravitreal injection into wild type mice eyes, we demonstrated that sepofarsen enters the target cells of the retina, including the photoreceptor cells. Sepofarsen has a long tissue half-life, with a current estimation of approximately 200 days based on data obtained in a non-human primate model for a closely related oligonucleotide.

**QR-421a and QR-411 for Usher Syndrome Type 2 and non-syndromic retinitis pigmentosa (NSRP)**

***Usher Syndrome Type 2 Background***

Usher syndrome is the leading cause of combined deafness and blindness. Patients with this syndrome generally progress to a stage in which they have very limited central and peripheral vision and moderate to severe deafness. Patients are usually born with moderate to severe hearing loss that may worsen over time. The retinal phenotype, known as retinitis pigmentosa, or RP, is characterized by photoreceptor degeneration that leads to progressive vision loss. The first visual symptoms typically appear during the second decade of life and start with night blindness due to the start of degeneration of rod photoreceptors. When rod degeneration progresses, patients lose their peripheral visual field until patients only have a residual central island of vision (tunnel vision). Progression of rod degeneration continues with the degeneration of cones which eventually results in complete blindness.

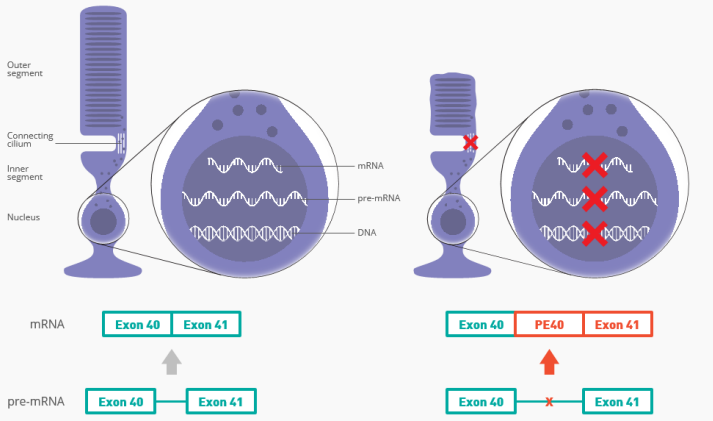
**Representation of exon 13 mutations causing Usher syndrome type 2**




In wild type cells usherin enables protein transport through the connecting cilium

In cells with the USH2A mutation usherin is not active, hampering protein transport over the cilium

**Representation of the PE40 mutation causing Usher syndrome type 2**




In wild-type cells usherin maintains photoreceptor structure and enables normal protein transport

In PE40 mutant cells protein transport is hampered and the outer segment degenerates

***Usher Syndrome Type 2 Genetics***

Usher syndrome type 2 is caused by mutations in the *USH2A* gene, encoding the protein usherin. Mutations in the *USH2A* gene can disrupt the production of usherin, a protein expressed in photoreceptors where it is required for their maintenance. Usherin is also expressed in the ear, where it is required for normal development of cochlear hair cells and hence, normal hearing. In the eye, defects in usherin cause RP. Mutations in *USH2A* can also cause NSRP, in which patients experience visual loss but do not suffer from hearing loss. Exon 13 mutations represent the most common mutations in the *USH2A* gene.

***Disease Prevalence and Diagnosis***

The diagnosis of the disease is based on clinical symptoms and ophthalmologic evaluations. A genetic screening can determine the specific mutation that is causing the disease. Although accurate prevalence figures do not exist, the number of patients with vision loss due to *USH2A* exon 13 mutations is estimated to be around 16,000 in the Western world. In Europe, the PE40 mutation is present in

approximately 3-7% of the total Usher syndrome type 2 population providing us with an estimate of 1,000 patients in the Western world. This number could be a considerable underestimate as many of these patients are unaware of the second disease causing allele following exome sequencing suggesting a causative mutation is intronic.

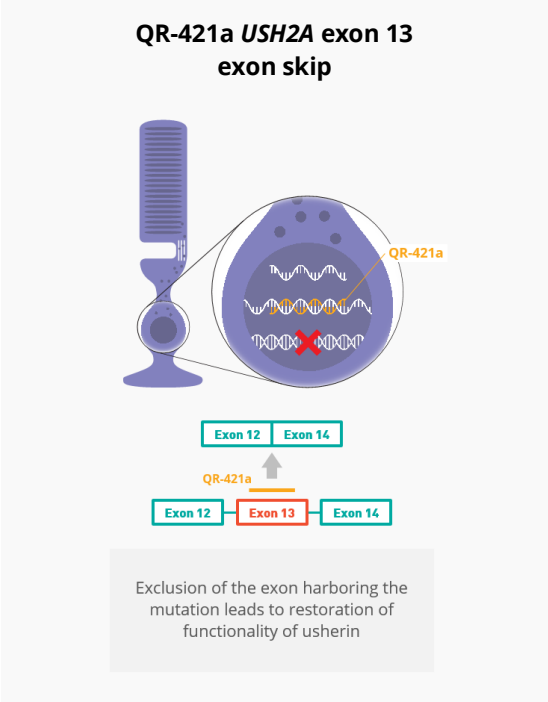
***Approaches for the treatment of Usher Syndrome Type 2***

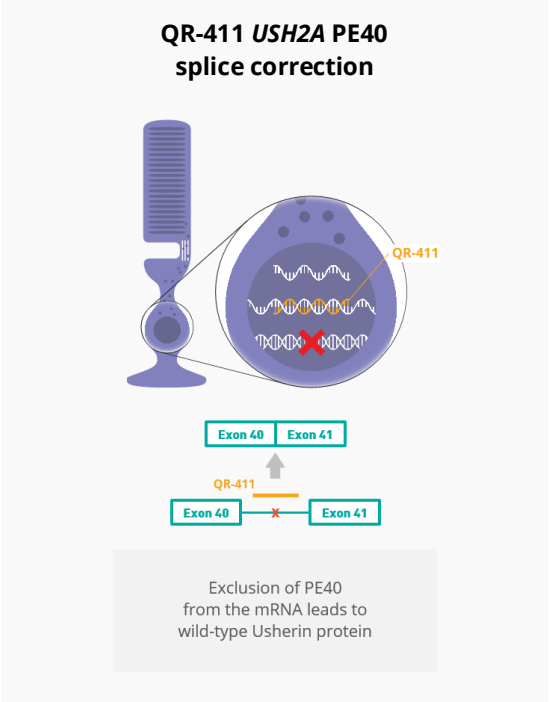
While the hearing deficit in patients with Usher syndrome type 2 can be at least partially mitigated using hearing aids or cochlear implants, there is no approved treatment for the vision loss associated with USH2A mutations and disease management is supportive in nature. Vitamin A and docosahexaenoic acid (DHA) supplementations have been proposed as pharmacological treatment options. Both therapies have shown a good safety profile but limited clinical benefit. We believe QR-421a and QR-411 are the only product candidates in development for the treatment of patients with RP caused by mutations in exon 13 or PE40 mutations in the *USH2A* gene. Due to the size of the USH2A protein, this type of RP is not amenable to a gene therapy approach. Also, given the disease affects both the peripheral and central retina, current limitations of the sub retinal procedure used in gene replacement and gene editing approaches, would make those approaches not amenable to targeting peripheral diseases.

***QR-421a and QR-411 for the Treatment of Usher Syndrome Type 2***

QR-421a is being developed as a treatment for RP caused by mutations in exon 13 of the *USH2A* gene. Mutations in exon 13, including the prevalent c.2299delG mutation, can disrupt the production of usherin. Usherin is required for photoreceptor maintenance. QR-421a aims to induce excision, or skipping, of exon 13 from *USH2A* mRNA leading to an in-frame deletion in the *USH2A* mRNA. Since exon 13 encodes for a repetitive part of the usherin protein, excision of exon 13 is expected to lead to a (partially) functional usherin protein. Because of the exon skipping approach, QR-421a is not specific to a single mutation but targets any mutation present in exon 13 of the *USH2A* gene.

Similar to the approach of sepofarsen, QR-411 is targeted at correcting the splicing of a pseudoexon. In patients the specific c.7595-2144A>G (PE40) mutation leads to the aberrant inclusion of this pseudoexon in the mature mRNA and consequently absence of a functional usherin protein. Correction of splicing with QR-411 can lead to restoration of normal, wild-type usherin protein.



QR-421a and QR-411 have received orphan drug designation from the FDA and EMA. QR-421a was also granted fast track designation by the FDA.

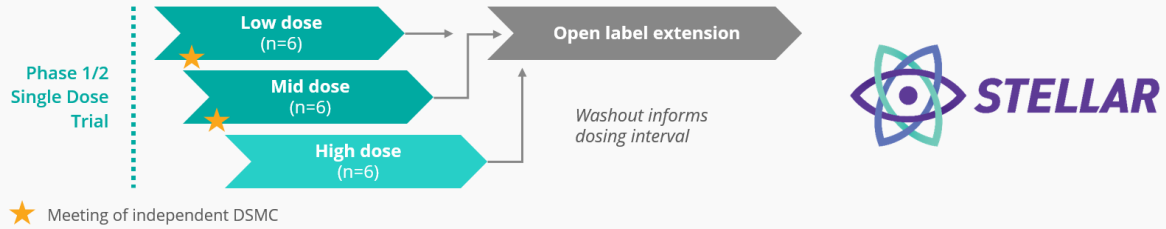
***Clinical Development of QR-421a***

We believe that results of preclinical studies provide support for the clinical development and therapeutic potential of QR-421a. The QR-421a clinical development program has been initiated with the first-in-human STELLAR study (PQ-421a -001), a Phase 1/2 study designed to evaluate the safety and tolerability of a single IVT injection of QR-421a in subjects with RP due to mutations in exon 13 of the *USH2A* gene. A potential dose response relationship and duration of effect following a single dose of QR-421a, based on improvements in retinal structure or visual field, will also be investigated to inform selection of dose level(s) and dosing intervals for subsequent studies. Improvement of visual function and retinal structure will be measured by several endpoints such as visual acuity (BCVA), visual field and optical coherence tomography (OCT). Changes in quality of life in the trial subjects will also be evaluated.

A total of 18 adult subjects are planned to be enrolled in three study cohorts, investigating three dose levels of QR-421a. Additional dose levels may be evaluated based on ongoing safety and efficacy data monitoring. Per dose cohort, a minimum of four subjects will be treated with QR-421a and a minimum of two subjects will receive a control sham-procedure. Once the last subject in a dose cohort reaches week 12, an interim analysis will be performed to evaluate available safety and efficacy data. QR-421a will be administered by unilateral intravitreal injection. Each subject will receive a single dose of QR-421a or sham procedure in their worse eye and will be assessed for safety, tolerability and efficacy at follow-up visits. An extension study, which would permit continued dosing of eligible subjects who complete PQ-421a-001, is planned.

An IND has recently been accepted by the FDA for the start of the first-in-human STELLAR study which will be conducted at expert sites in North America and Europe. In March 2019, the first patient was dosed in the Phase 1/2 STELLAR clinical trial for QR-421a in patients with Usher syndrome type 2 or non-syndromic retinitis pigmentosa (RP).

**Design of Phase 1/2 STELLAR Study of QR-421a**



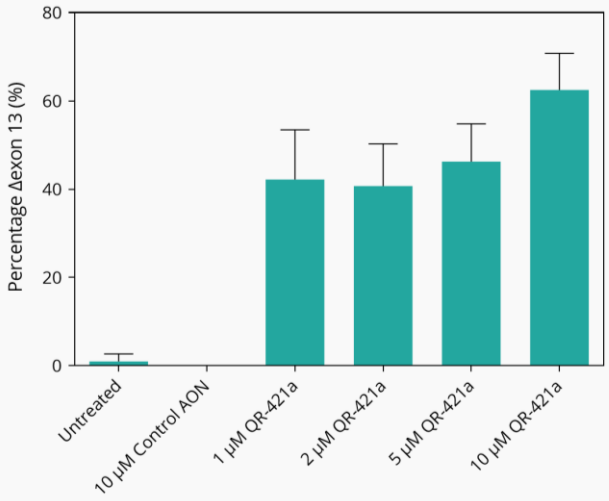

Beyond QR-421a and QR-411 we have an additional discovery-stage program, QRX-461, for another mutation in *USH2A*.

***Preclinical evidence for QR-421a***

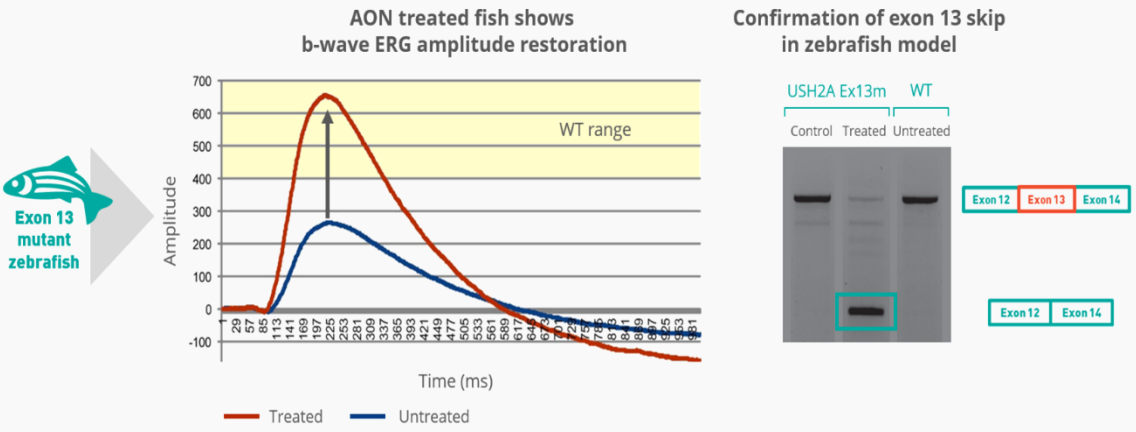
In preclinical data we observed:

- QR-421a induced an *in vitro* concentration-dependent *USH2A* exon 13 skip in human retinal organoids
- Translation of *ush2a* Δexon 13 mRNA into functional Ush2a protein, as confirmed by visualization of protein in the photoreceptors and ERG b-wave restoration in zebrafish model; and
- QR-421a showed rapid clearance from vitreous with prolonged retention and activity in retina in non human primates

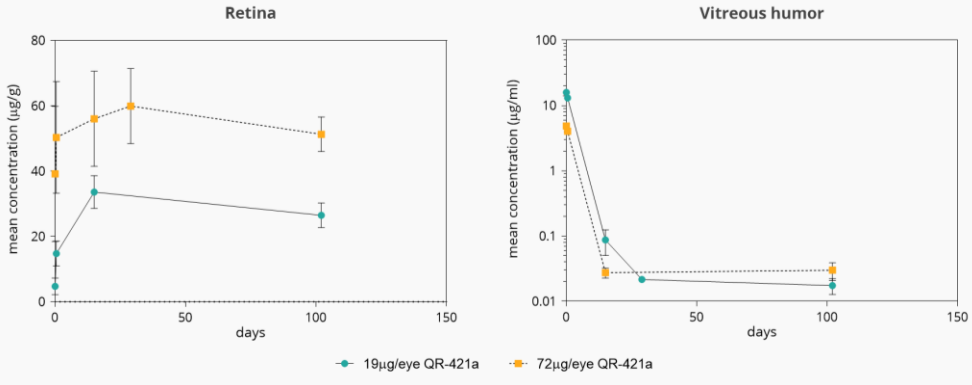
**Concentration-Dependent Increase of USH2A Exon 13 Skip After One Month of Exposure to QR-421a in c.2299delG Homozygous Patient Retinal Organoids**




**Exon-13 splicing oligos restore ERG in exon-13 mutant fish**




**Pharmacokinetics in non human primates**



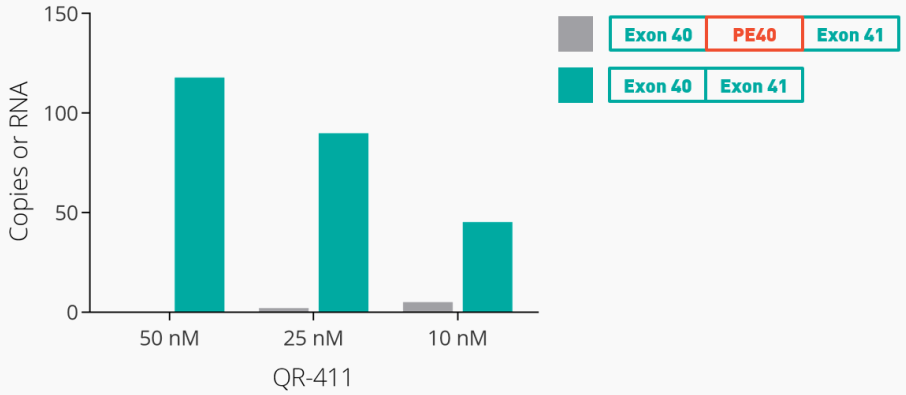
***Clinical Development of QR-411***

QR-411 is currently undergoing IND-enabling studies. We plan to advance the QR-411 program towards a Phase 1/2 clinical study in 2020. The clinical trial will consist of a single-dose study to determine safety, tolerability and efficacy.

***Preclinical evidence for QR-411***

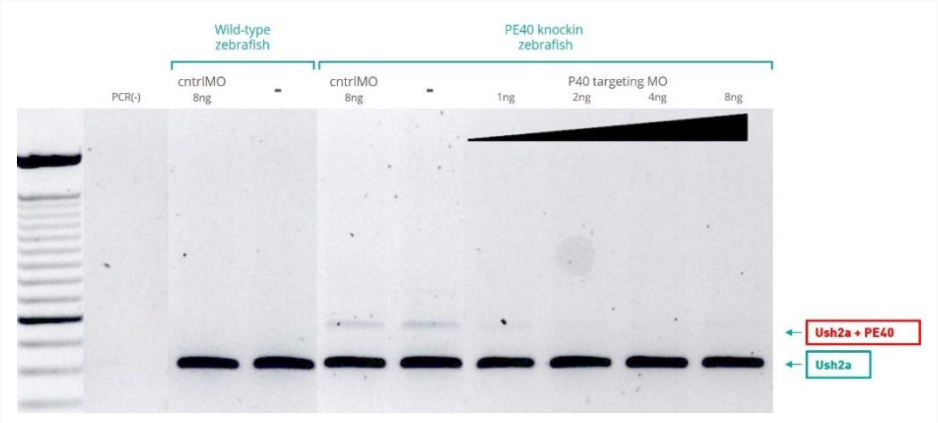
- QR-411-effected splice correction has been observed in patient fibroblasts and two dimensional photoreceptor progenitor cells derived from primary fibroblasts of an *USH2A* c.7595-2144A>G (PE40) compound heterozygous patient.
- QR-411 demonstrates splice correction by the exclusion of human PE40 in a humanized *Ush2A* zebrafish model.

**QR-411 increases wild type *USH2A* mRNA**




(1) Expression of wild type (blue bars) and PE40 (black bars) mRNA in a compound heterozygous patient fibroblast cell line carrying one allele containing the PE40 mutation and the other allele an exon 13 mutation (c.2391_2392del) after treatment with 10, 25, or 50 nM QR-411.

**QR-411 splice correction of pseudoexon 40 in mutant zebrafish**



**QR-1123 for autosomal dominant retinitis pigmentosa (adRP)**

***adRP Background***

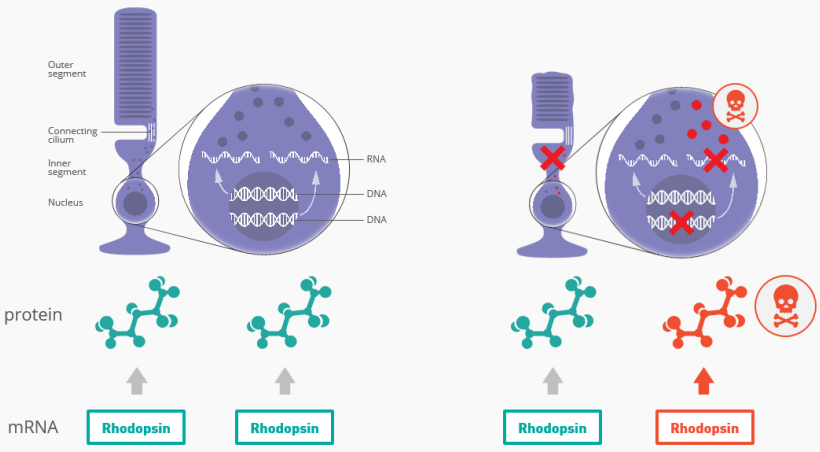
Retinitis pigmentosa (RP) is a group of hereditary retinal diseases in which patients first experience loss of night vision in childhood followed by loss of peripheral vision in young adulthood, and central vision in later life which ultimately progresses to complete blindness. The worldwide prevalence of RP is about 1 in 4000 for a total of more than 1 million affected individuals. The disease can be inherited as an autosomal-dominant (about 30–40% of cases), autosomal-recessive (50–60%), or X-linked (5–15%) trait.

Autosomal-dominant RP (adRP) is characterized by abnormal, diminished or absent a- and b-waves in the electroretinogram (ERG), reduced peripheral vision (visual field) and the presence of visual defects such as reduced visual acuity and poor photo- and contrast sensitivity. Symptoms typically start in the early teenage years, which include night blindness and reduction of the peripheral vision due to the degeneration of the rod photoreceptors. As the disease progresses, cone photoreceptors are also affected, which translates into loss of central vision and eventually complete blindness in adulthood.

***adRP Genetics***

Mutations in more than 25 genes can cause adRP, but most commonly mutations are found in the rhodopsin (*RHO*) gene, accounting for approximately 25% of adRP cases. The rhodopsin protein is a light sensitive pigment that is present in the rod photoreceptors in the retina. Rhodopsin, when exposed to light, undergoes conformational changes that are converted into an electrical signal which is sent to the brain where it is interpreted as vision. In the United States, the most prevalent mutation associated with adRP is the P23H mutation (also known as c.68C>A) in the RHO gene. The mutant P23H rhodopsin protein is misfolded and toxic to the rod photoreceptor cells causing loss of vision. Although some wild-type protein is being made, there is substantial evidence that the mutant P23H rhodopsin protein elicits a dominant-negative mechanism, such that it diminishes the function of the wild-type protein.

**Representation of the p.Cys998X mutation causing LCA10**




Healthy people inherit two wild type copies of the rhodopsin gene

P23H mutant rhodopsin is misfolded and toxic, causing progressive loss of rods

***Disease Prevalence and Diagnosis***

In the United States the P23H mutation in the *RHO* gene is the most common mutation causing adRP and affects approximately 2,500 patients. The diagnosis of adRP is based on clinical symptoms and ophthalmologic evaluations. A genetic screening can determine what specific mutation is causing the disease.

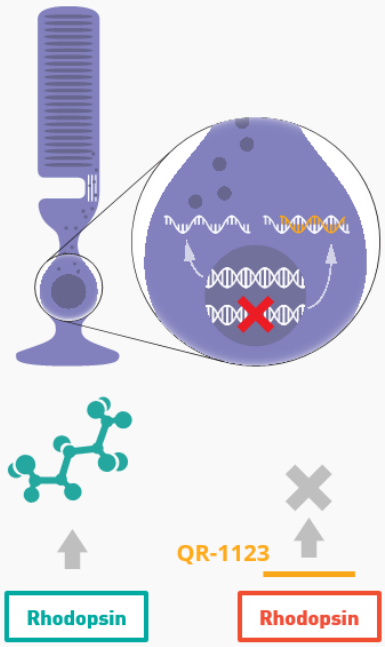
***Approaches for the treatment of adRP***

We believe QR-1123 is the only candidate in development for the treatment of patients with adRP caused by the P23H mutation and disease management is currently supportive.

***QR-1123 for the treatment of adRP***

QR-1123, discovered by Ionis Pharmaceuticals and in-licensed by ProQR in 2018, is designed for the treatment of P23H adRP. QR-1123 is a gapmer that aims to suppress the formation of the mutant protein by selectively targeting the mutant RNA and causing its destruction by RNase H1 cleavage without affecting the wild-type RNA. With reducing the mutant RNA we believe the toxicity-induced loss of the photoreceptors and subsequent loss of vision can be stopped or potentially reversed.

**QR-1123 for adRP, mutant specific knock-down of P23H mRNA**




QR-1123 suppresses P23H mRNA with an allele specific mechanism

***Clinical Development of QR-1123***

Currently, the QR-1123 program is undergoing the final preparation stages for IND submission. We plan to advance the QR-1123 program towards a Phase 1/2 clinical trial during 2019.

***Preclinical evidence for QR-1123***

*QR-1123 is specific for P23H mutant RNA*

In vitro and in vivo experiments have been performed to study the specificity of QR-1123 for the P23H mutant RNA. Cell models expressing wild-type or P23H mutant human RHO were used to determine the selectivity of QR-1123 induced knock-down of P23H mRNA. QR-1123 was observed to selectively target the human P23H mutant rhodopsin mRNA, whilst sparing the human wild-type mRNA (Figure 2, left panel).

Mice expressing either human wild-type or P23H RHO were used to determine the ability of QR-1123 to selectively target the P23H mutant mRNA in vivo following intravitreal delivery. The mice were treated with either QR-1123 or a control and the other (contralateral) eye was injected with saline solution and used as a comparator control. As expected, in mice expressing wild-type RHO, no difference was observed between the two study groups (Figure 2, right panel) while mutant P23HRHO mRNA was reduced after a single QR-1123 injection in the hP23HTg mice eyes (Figure 2, center panel) confirming the specificity for the P23H allele.

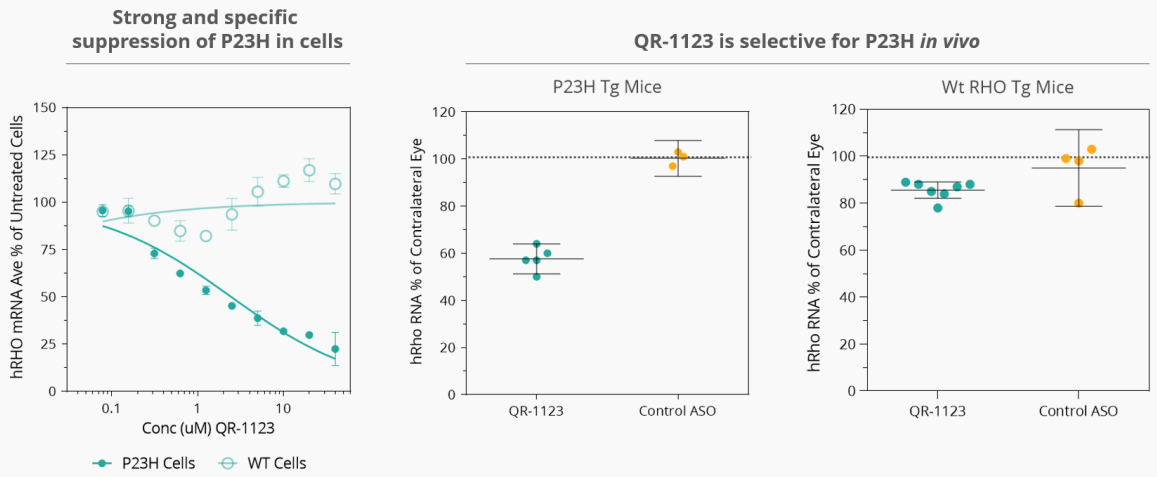



Figure 2: Transgenic mice expressing human P23H RHO treated with QR-1123 or a control; data are presented as percent of contralateral eye PBS-treated RNA level. Right Panel: Transgenic mice expressing human wild-type (WT) RHO treated with QR-1123 or a control; data are presented as percent of contralateral eye PBS-treated RNA level.

### *QR-1123 surrogate improves ERG in P23H rat model*

A rat model of P23H adRP undergoes degeneration and photoreceptor cell loss that is generally characteristic of human P23H adRP although the degeneration in these rats is more aggressive than is observed in humans. Approximately 25% of photoreceptor cells are lost by Day 15 in these animals, and there are few functional photoreceptor cells by 29 weeks of age. Rats received saline in their left eyes and either QR-1123 surrogate or control intravitreal treatment in the right eyes once on Day 10 and again on Day 21 after birth. On Day 42 (32 days following the first injection) the rats' photoreceptor cell response was measured by ERG. The rats given QR-1123 surrogate had an improved scotopic a-wave response amplitude at all stimulus intensities (Fig. 3, left panel). This improved response was not observed in the control-treated eyes (Fig. 3, left panel).

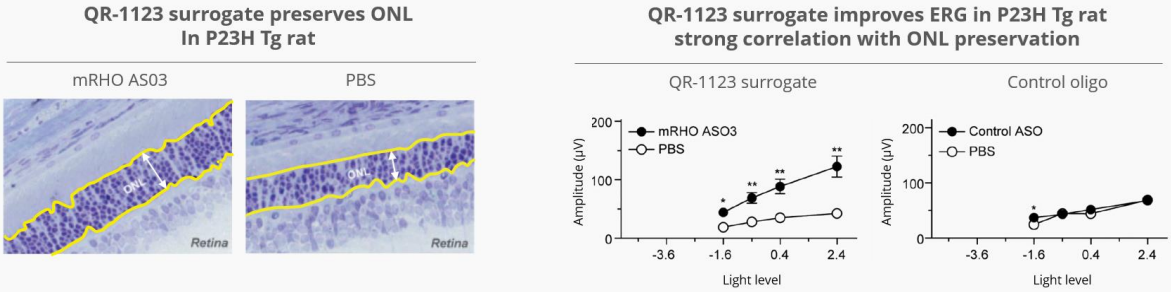



Figure 3: ONL preservation and ERG improvement after QR-1123 treatment. Left Panel: Representative retinal micrographs of P23H-1 rhodopsin transgenic rat eyes from the PBS or QR-1123 surrogate-treated eye 30 days post IVT injection. Right Panel: Improved ERG response in P23H-1 transgenic rats after a single QR-1123 surrogate treatment with IVT injections at P13 (A) or P14 (B), with ERG measurements made at P48. (A, B). Amplitude versus stimulus intensity curves for scotopic a-waves (circles). The scotopic a-waves of eyes injected with QR-1123 surrogate were significantly greater than PBS-injected contralateral eyes while eyes treated with control were similar to those of PBS-injected contralateral eyes (t-test; *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001). In the data points without apparent error bars, the error bars are obscured by the symbol.

### *QR-1123 reduces retinal degeneration in mouse model*

A mouse model of P23H adRP shows degeneration of photoreceptor cells in the retina (reduced cell rows in the outer nuclear layer (ONL)) at about 3 months of age. A single intravitreal (IVT) administration of QR-1123 retarded the progressive retinal degeneration, as measured at 60 days after the single treatment (Figure 4,

top panel). Importantly, the activity was observed throughout all regions of the retina (Figure 4, lower panel). This shows that QR-1123 has the capability to stop retinal degeneration and indicates that a mechanism based on inhibition of the formation of toxic mutant version of rhodopsin protein has the potential to improve a clinically relevant functional outcome in RP.

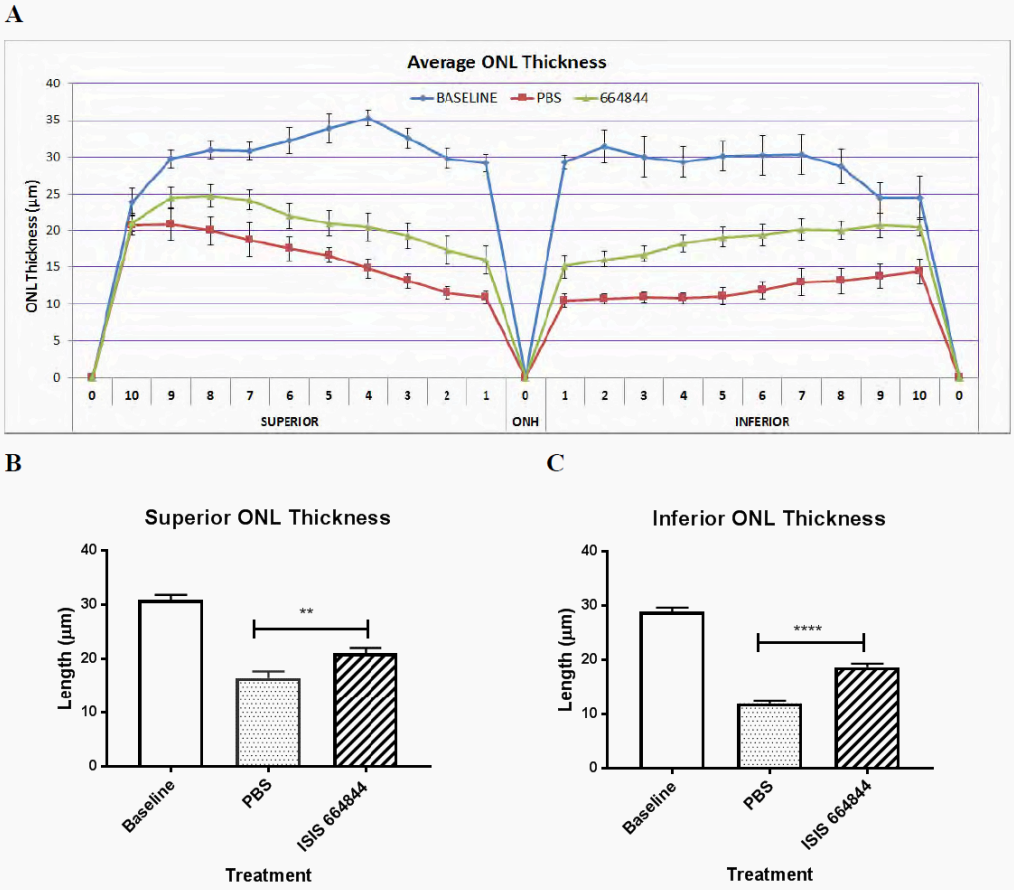



Figure 4: Preservation of ONL in a Tg mouse model after treatment with QR-1123. Top panel: Depicted is a spider diagram of the outer nuclear layer measurements of the entire retina of eyes treated with either PBS (red line) or QR-1123 treated eyes (Green line). Lower Left panel: Average superior region ONL thickness at baseline and in PBS and QR-1123 treated mice. Lower Right panel: Average inferior region ONL thickness at baseline and in PBS and QR-1123 treated mice. Two-tailed t test; **p < 0.01, ****p<0.0001.

**Human resources**

At ProQR we have set ourselves the immense task of developing drugs that will potentially transform the lives of patients suffering from severe genetic diseases like cystic fibrosis, Leber's congenital amaurosis, and epidermolysis bullosa. To make this happen we demand the utmost of ourselves. We actively create a caring atmosphere filled with fun and joy, in which we love to work and maintain productive and happy lives. At ProQR we foster empowerment, self development, creativity and a sense of community.

We are a supportive, ingenious and persistent team that does things different. We're passionate and driven to change the lives of patients and their loved ones.

**Corporate social responsibility**

It is required by regulatory authorities to demonstrate the safety and efficacy of a new drug in animals, before its efficacy and safety can be tested in humans. ProQR attaches great importance to the welfare of

animals in our preclinical studies for reasons of ethics, quality, reliability and applicability of scientific studies. For conducting high quality (scientific) animal research, animal welfare is a prerequisite. By actively pursuing the 3R principles (Reduce, Refine and Replace), ProQR is committed to reduce the number of animals needed, minimize discomfort and pain of animals used, and use alternatives to animal research whenever possible.

Animal experiments will be performed only if there are no alternatives such as performing in silico, in-vitro or ex-vivo studies. On a case by case basis, study designs of animal studies will be evaluated with the aim to identify opportunities for reduction of the number of animals needed to achieve the objectives of the study. By the conduction of small pilot (tolerability) studies first, or by using new technologies to achieve adequate statistical power without increasing the number of animals, by combining studies and by improving the use of toxicokinetic and modelling data to optimize dose selection, ProQR further pursues the ambitions to reduce, refine and replace animal studies. Approval by the (institutional or national) animal care and use committees is required prior the execution of in vivo studies.

External collaborators contracted for the execution of our in-vivo preclinical studies (contract research organizations, CROs) are selected based on their expertise, quality and accreditations for laboratory animal care and welfare. CRO facilities are audited in person prior contracting to ensure that the housing, husbandry and animal welfare complies with the highest international standards. Personnel responsible for housing, husbandry and care of the animals must have received adequate and relevant documented education.

In 2015 ProQR became part of an interdisciplinary consortium with Utrecht University (Faculty of Veterinary medicine and Ethics Institute), Radboud University (Medical Center, SYRCLE) and another private company, partly financed by The Netherlands Organization for Scientific Research, Responsible Innovation grant. The project proposes a more integrated approach towards innovation in the field of animal testing and focuses on translational strategies. ProQR is involved in the work package that aims to deliver step stones for practical guidelines to build robust translational strategies, to design innovative experiments (including animal models) for cystic fibrosis and other rare genetic diseases.

**Manufacturing and Supply**
We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of any of our product candidates. We currently contract with drug product manufacturers for the production of sepofarsen solution for intravitreal injection, QR-421a solution for intravitreal injection and QR-1123 for intravitreal injection, and we expect to continue to do so to meet the planned clinical requirements of our product candidates.

Currently, each of our active ingredients for our manufacturing activities are supplied by single source suppliers. We have agreements for the supply of such active ingredients with manufacturers that we believe have sufficient capacity to meet our demands. In addition, we believe that adequate alternative sources for such supplies exist. We typically order clinical supplies and services on a purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements.

We do have clinical manufacturing processes developed at a back-up GMP manufacturer. Manufacturing is subject to extensive regulations that impose various procedural and documentation requirements, which govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance, amongst others. The contract manufacturing organizations we use manufacture our product candidates under cGMP conditions. cGMP is a regulatory standard for the production of pharmaceuticals that will be used in humans.

**Competition**

The pharmaceutical industry is highly competitive and subject to rapid and significant technological change. Our potential competitors include large pharmaceutical, biotechnology, specialty pharmaceutical, and generic drug companies, academic institutions, government agencies and research institutions. Key competitive factors affecting the commercial success of our product candidates are likely to be efficacy, safety and tolerability profile, delivery, reliability, convenience of dosing, patient recruitment for clinical studies, price and reimbursement. Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA, EMA and other regulatory approvals of products and the commercialization of those products. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a small number of our competitors. Accordingly, our competitors may be more successful than we may be in obtaining FDA or EMA approval for therapies and achieving widespread market acceptance. Our competitors' products may be more effective, or more effectively marketed and sold, than any product candidate we may commercialize and may render our therapies obsolete or non-competitive before we can recover development and commercialization expenses.

Our competitors are working on similar technologies in the field of RNA repair and RNA editing, but also in the field of gene editing and gene therapy as well as other types of therapies, such as small molecules, protein replacement or antibodies. The industry targeting hereditary ophthalmology indications is driven by gene therapy (Spark Therapeutics/Genable, AGTC, Sanofi, Oxford Biomedica), gene editing (Editas Medicine; ciberer, OxfordBioMedica and Harvard Medical School), and other approaches (Wave life sciences).

In the field of DEB, a number of companies are seeking to identify and develop drugs. There are four general clusters of potential disease modifying treatments for RDEB: autologous gene therapies (Krystal Biotech, Abeona, Fibrocell, King's Collegeand Holostem Terapie Avanzate), allogeneic cell therapies (Allogeneic Cell Therapies, University of Minnesota, Anterogen and King's College), RNA modulation therapies (University of Southern California) and protein replacement therapies (Phoenix Tissue Repair). In regards to palliative treatments, the therapies that are currently under development are symptomatic and focus on reducing a secondary EB manifestation (Amicus, Amryt, and Tarix Orphan).

**Main financial developments**

***Financial position***

In 2018, our operating costs were in line with last year while our liquidity and solvency went up due to an increase in cash and cash equivalents. At December 31, 2018, ProQR's cash and cash equivalents amounted to € 105,580,000 compared to € 48,099,000 at December 31, 2017. During the year 2018, operating cash used amounted to € 28,493,000, compared to € 34,951,000 in 2017. Total equity increased to € 92,685,000.

As at December 31, 2018, we had borrowings of € 9,386,000, which consisted of borrowings from a government body and convertible loans. Based on the current state of affairs and existing funding, taking into account our current cash position and projected cash flows, it is justified that the financial statements are prepared on a going concern basis.

***Income statement***

We have generated losses since our formation in February 2012. For the years ended December 31, 2018 and 2017, we incurred net losses of € 37,086,000 and € 43,675,000, respectively. As at December 31, 2018, we had an accumulated deficit of € 155,443,000. We expect to continue incurring losses for the foreseeable future as we continue our pre-clinical studies of our product candidates, continue clinical development of our product candidates sepofarsen and QR 421a, advance QR-1123 into clinical development, increase investments in our other research programs, apply for marketing approval of our product candidates and, if approved, build a sales and marketing infrastructure for the commercialization of our product candidates. To date, we have not

generated any revenues from royalties or product sales. Based on our current plans, we do not expect to generate royalty or product revenues for the foreseeable future.

Other income is incidental by nature. In 2015, the European Commission (EC) through its Horizon 2020 program awarded us and our academic partners a grant of € 6 million to support the clinical development of eluforsen, formerly known as QR-010 (ProQR: € 4.6 million). On February 9, 2018, the Company entered into a partnership agreement with Foundation Fighting Blindness (FFB), under which FFB has agreed to provide funding of $ 7.5 million for the pre-clinical and clinical development of QR-421a for Usher syndrome type 2A targeting mutations in exon 13. On June 5, 2018, the Company entered into a partnership agreement with EB Research Partnership (EBRP) and EB Medical Research Foundation (EBMRF) under which EBRP and EBMRF have agreed to provide funding of $ 5.0 million for the clinical development of QR-313 for Dystrophic Epidermolysis Bullosa targeting mutations in exon 73. Other income amounted to € 5,761,000 compared to € 1,495,000 in 2017. We expect to continue generating other income from new grant applications in 2019.

Research and development costs amount to € 29,514,000 in 2018 compared to€ 31,153,000 in 2017. These research and development costs comprise allocated employee costs including share-based payments, the costs of materials and laboratory consumables, the costs for production of clinical and pre-clinical compounds and outsourced activities, license and intellectual property costs and other allocated costs. These costs were primarily related to our product candidates, sepofarsen, QR-313 and QR-421a, and our innovation unit. Our research and development expense is highly dependent on the development phases of our product candidates and is expected to stay at the same level, although it may fluctuate significantly from period to period.

Costs were incurred for the advancement of our pipeline, which included clinical development of sepofarsen eluforsen and QR-313, preclinical development of QR-421a and progress of our innovation programs. The variances in research and development costs between the years ended December 31, 2018 and 2017 are mainly due to:

- costs we incurred on clinical trials for sepofarsen, particularly in 2018;
- costs we incurred on clinical trials for eluforsen, particularly in 2017, decreasing in 2018 after completion of the clinical studies. No additional clinical study activities are planned;
- slightly decreased staff costs. The number of full-time equivalent employees working on research and development decreased from 96 at December 31, 2017 to 89 at December 31, 2018;
- In November 2018, the Company issued 112,473 shares in the aggregate amount of $ 2.5 million, at $ 22.23 per share to Ionis. Under the terms of the agreement made an upfront payment in ordinary shares to its common stock, to Ionis upon signing the worldwide license agreement. The Company was granted an exclusive worldwide license to QR-1123 and relevant patents. The Company will also make future milestone payments, certain of which will be made in equity and others in cash or equity at the company's discretion, and royalties on net sales of 20% through the royalty term.
- costs for externally conducted studies, including various in vivo studies, proof of concept studies and dose ranging and toxicity studies conducted in connection with the development of our product candidates;
- costs for the production of QR-313 and QR-421a compounds in 2017, including the costs of GMP batches in preparation of our clinical studies;
- laboratory costs including purchases of compounds and laboratory materials used by the research and development staff in proportion to the decrease in the number of employees, and increased costs for the use of laboratories;
- project-related consultancy costs, including regulatory and intellectual property support; and
- decreased share-based compensation, reflecting grants of share options to research and development staff made after we adopted our Option Plan in September 2013.

General and administrative costs increased to € 12,540,000 in 2018 from € 10,840,000 in 2017. These general and administrative costs comprise employee costs, office costs, general consultancy costs and other costs. As a public company, we face increased legal, accounting, administrative and other costs and expenses. The increase was primarily related to:

- increased office and general costs, including office rent, information technology and communication costs, travel costs and office consumables, as well as costs to improve our internal control environment;
- increased costs for legal support, accounting and other consultancy costs, including costs incurred in preparation of offerings in 2018; and
- decreased share-based compensation, reflecting grants of share options to non-research and development staff made after we adopted our Option Plan in September 2013.

In 2018 share-based compensation amounted to € 3,224,000, compared to € 4,024,000 in 2017. Net financial expenses amounted to € 792,000, compared to € 3,175,000 in 2017. Financial income & expenses mainly result from foreign exchange differences on cash denominated in U.S. dollars and can fluctuate significantly. The Company operates a foreign exchange policy to manage the foreign exchange risk against the functional currency based on the Company's cash balances and the projected future spend per major currency.

**Outlook**

In 2019, we continue to invest in our organization, while we continue our pre-clinical studies and clinical development of our product candidates and increase investments in our other research programs. Our goal is to realise this at our current operational level. A significant increase in headcount is not expected. We believe we have sufficient cash to fund these expenses and to prepare the Company for future growth. Given the development stage of the Company, we do not anticipate revenues in the foreseeable future.

Leiden, March 28, 2019

On behalf of the Management Board,

Daniel de Boer
CEO

# Supervisory Board Report

ProQR Therapeutics has chosen for its governance structure to be a so-called two-tier system. In such a setting the Supervisory Board supervises and advises the Management Board in performing their management tasks and setting the strategy of the Company. The Supervisory Board as well as its individual members act in the interests of ProQR, its business and development and all its stakeholders.

The Supervisory Board and its sub-committees held frequent and productive interactions with the Executive Board. Where appropriate, decision taking was endorsed by the Supervisory Board and matters of both short term as well as long term strategic importance were discussed in a constructive and transparent manner.

Below is a more specific description of the Supervisory Board's activities during the financial year 2018 and other relevant information on its functioning.

**Activities of the Supervisory Board**
The Supervisory Board and the Board of Directors met multiple times during 2018 and have held various additional informal meetings and telephone conferences, both collectively and individually. During these meetings, the progress of the various projects, the main risks of the business, the funding and the strategic direction of the Company were discussed. In addition, a two-day off-site was held during which the long-term strategy of the company was discussed. The Supervisory Board meetings were very well attended and the Committees reported back on their activities to the full Supervisory Board on a regular basis.

**Committees of the Supervisory Board**
We have an audit committee, a compensation committee and a nominating and corporate governance committee. We have adopted a charter for each of these committees.

***Compensation Committee***
The Compensation Committee met 2 times in 2018.

*Compensation report 2018*
In June 2016, the General Meeting of Shareholders adopted our Compensation Policy. This Compensation Policy also applied to the financial year 2018 and will apply to subsequent years. Attraction and retention of world class talent is a prerequisite for the success of ProQR and competitive compensation plays a vital role in our ability to achieve this. The Compensation Committee elected to offer compensation for all employees including the Management Board into a fixed annual salary and a variable, performance related, short and long term incentive element. The Compensation Policy is designed based on the following principles:

- Three compensation pillars consisting of:
  - Annual Base Salary;
  - Short Term Incentive (annual cash bonus);
  - Long Term Incentive (Stock Option Plan);
- Flexibility: The Compensation Policy should provide flexibility to allow the Supervisory Board, acting on the recommendation of the Compensation Committee, to reward the Management Board in a fair and equitable manner;
- This Compensation Policy should drive the right kind of management behavior, discourage unjustified risk taking and minimize any gaming opportunity;
- This Compensation Policy should pay for performance, considering not only the measurable financial performance of / or milestones achieved by the Company, but also, where appropriate, the efforts made

by the Management Board, individually and as a group, in managing the Company. For the variable components, the Compensation Committee performs an analysis of the possible outcomes under different scenarios;
- Design of the Compensation Policy shall be based on current legislation applicable in the Netherlands;
- This Compensation Policy shall foster alignment of interests with shareholders;
- The pension of the Management Board shall be based on the defined contribution system; and
- Pay differentials and position within the Company are considered and evaluated regularly.

*Annual Base Salary*
The Compensation Committee reviewed the annual base salary of the Management Board taking into consideration the Compensation Reference Group as contained in the Compensation Policy. Based on this review the annual base salary levels for 2019 have been set at € 404,000 for the CEO, Daniel de Boer. René Beukema resigned as per the end of 2018 and received a severance payment of € 324,000.

*Short Term Incentive*
The Compensation Committee reviewed the performance of the Company during 2018 in comparison to the objectives and reviewed the achievements of the members of the Management Board versus their personal objectives.

Based on the recommendation of the Compensation Committee, the Supervisory Board decided late 2018 that the Company has achieved 125% of the objectives that had been set to determine the individual bonus awards for the year 2018. For 2018 the individual bonus has been set at € 281,000 for Daniel de Boer and at € 134,000 for René Beukema. Final installment of these bonuses will be paid in cash in the first quarter of 2019.

*Long Term Incentive*
Based on the recommendation of the Compensation Committee, the Supervisory Board decided to grant stock options in 2018 to the CEO, Daniel de Boer and the chief corporate development officer and general counsel, René Beukema. Based on this decision stock options with an exercise price of € 2.74 have been granted with respect to 379,285 shares to the CEO, Daniel de Boer and 140,932 shares to the chief corporate development officer and general counsel, René Beukema.

*Pensions*
The pension contributions paid during 2018 amount to € 9,000 for the CEO, Daniel de Boer and € 16,000 for the chief corporate development officer and general counsel, René Beukema.

*Internal pay ratio*
The internal pay ratio between the average pay of our employees and our Management Board is calculated based on the average remuneration based on short term and long term incentives. The pay ratio is 8:1 for 2018.

*Supervisory Board remuneration*
In June 2016, our shareholders approved an amended compensation policy whereby members of our Supervisory Board receive board fees of € 25,000 per year and the chairperson receives board fees of € 30,000 per year. In addition, each board committee chairperson receives € 5,000 per year for service on such committee (except for the chairperson for the nominating committee who receives € 3,000), and each other member of a board committee receives € 3,000 per year for service on such committee. On top of that, Supervisory Board members were granted options as set out in Note 23 to the financial statements or $ 55,000 in cash.

***Nominating and Corporate Governance Committee***

The Supervisory Board assessed its composition in 2018. It was concluded that the composition of the Supervisory Board is satisfactory and appropriate for current the phase of the company. Looking forward the supervisory board expressed a desire to seek three new candidate members over the next 18 months with knowledge and/or expertise of rare disease, ophthalmology, and/or commercialization and a candidate who is capable of taking over the chair position of the audit committee.

***Audit Committee***

The audit committee met 5 times in 2018. Main topics addressed were the quarterly results, financial risk management, compliance and SOx implementation, the audit plan and management letter of the external auditor, cash management, tax and corporate governance.

The audit committee also reviewed ProQR's annual financial statements, including non-financial information, prior to publication thereof. These financial statements for 2018 have been audited and provided with an unqualified opinion by our external auditor, Deloitte Accountants B.V., and were extensively discussed with the auditors in the meetings of the Supervisory Board, Audit Committee and Management Board on March 26, 2019. The Supervisory Board is of the opinion that the Financial Statements 2018 meet all requirements and recommends that the Annual General Meeting of Shareholders adopts the financial statements and the appropriation of net result proposed by the Management Board.

The Company's external auditor attended all Audit Committee meetings. The Audit Committee evaluates the performance of Deloitte as independent external auditor annually. Due to the limited size of the Company, it was concluded that there was currently no need to appoint an internal auditor.

The Supervisory Board is responsible for the quality of its own performance and it discusses, once a year on its own, without the members of the Management Board present, both its own functioning and that of the individual members, and the functioning of the Management Board and that of its individual members. The Supervisory Board discussed its functioning and competencies and concluded that it's functioning and competencies are appropriate for the current phase of the company, but expressed an intent to seek new candidates as described above. The performance and composition of the Management Board were also found to be adequate. We feel the additional efforts of all staff at ProQR form a strong foundation for the success and growth of the Company and all milestones reached this past year. Therefore, we would like to express our thanks to the members of the Management Board, senior management and all other employees for their contribution and performance during the year. The Supervisory Board is grateful for René Beukema's invaluable contributions and dedication to ProQR as a member of our management Board. His commitment has been exemplary for all ProQRians. We thank our shareholders for their continued support.

Leiden, March 28, 2019

On behalf of the Supervisory Board,

Dinko Valerio
Chairman

# Corporate Governance

ProQR values the importance of complying with Corporate Governance regulations. At the same time, the Board of Directors is of the opinion that certain deviations from the provisions of the new Dutch Corporate Governance Code 2016 ("DCGC" or "the Code") are justified, in view of our activities, our size and the specific circumstances in which we operate. In such cases, which are mentioned in this corporate governance statement, we apply the "comply or explain" principle.

Deviations from certain aspects of the Code, when deemed necessary in the interests of the Company, will be disclosed in the Annual Report. Most deviations are justified due to our Company being listed in the United States with most of our investors being outside of the Netherlands, as well as to the international business focus of our Company. As a Company listed on NASDAQ, we comply with NASDAQ's corporate governance listing standards, except for instances where we follow our home country's corporate governance practices in lieu of certain NASDAQ's standards as explained below, as NASDAQ investors are more familiar with NASDAQ's rules than with the Code.

In this report, the Company addresses its overall corporate governance structure and states to what extent and how it applies the principles and best practice provisions of the Code. This report also includes the information which the Company is required to disclose pursuant to the Dutch governmental decree on Article 10 Takeover Directive and the governmental decree on Corporate Governance.

Substantial changes in the Company's corporate governance structure and in the Company's compliance with the DCGC, if any, will be submitted to the General Meeting of Shareholders for discussion under a separate agenda item. The Supervisory Board and the Management Board, which are responsible for the corporate governance structure of the Company, are of the opinion that the principles and best practice provisions of the DCGC that are addressed to the Management Board and the Supervisory Board, interpreted and implemented in line with the best practices followed by the Company, are being applied.

The full text of the DCGC can be found at the website of the Monitoring Commission Corporate Governance Code (www.mccg.nl) and for an overview of our conformity with the Code the following documents are available at our website (www.ProQR.com): audit committee charter, compensation committee charter, nominating and corporate governance committee charter and our code of business conduct and ethics.

**Management Board**
ProQR is dedicated to improve the lives of our patients and their loved ones through the development of RNA therapies for severe genetic orphan diseases. ProQR has a focus on patients with LCA, Usher and EB. The expectations and interests of our stakeholders is a key reference point in establishing our long term strategy.

The Management Board's role is to develop long term value creation by means of a strategy to pursue the long term success of ProQR. The strategy contains multiple elements linked to the new Corporate Governance Code:

- Implementation and feasibility;
- Business model applied by the company;
- Opportunities and risks;
- Operational and financial objectives;
- Interest of shareholders;
- Any other relevant aspects such as environment, charity and patient organizations.

The Management Board executes the strategy by assuming the authority and responsibilities assigned to it by Dutch corporate law and by combining expertise and experience with entrepreneurial leadership. The Management Board operates under the supervision of the Supervisory Board. The Management Board is required to:

- Keep the Supervisory Board informed in a timely manner in order to allow the Supervisory Board to carry out its responsibilities;
- Consult with the Supervisory Board on important matters; and
- Submit important decisions to the Supervisory Board for its approval.

Our Management Board may perform all acts necessary or useful for achieving our corporate purposes, other than those acts that are prohibited by law or by our articles of association. The Management Board as a whole and any Management Board member individually, are authorized to represent us in dealings with third parties.

Under our articles of association, the number of Management Board members is determined by the Supervisory Board, and the Management Board must consist of at least one member. The Supervisory Board elects a CEO from among the members of the Management Board.

Members of the Management Board are appointed by the general meeting of shareholders upon a binding nomination of the Supervisory Board. Our general meeting of shareholders may at all times deprive such a nomination of its binding character by a resolution passed by at least two-thirds of the votes cast representing more than 50% of our issued share capital, following which our Supervisory Board shall draw up a new binding nomination.

Our Management Board rules provide that, unless the resolution appointing a Management Board member provides otherwise, members of our Management Board will serve for a maximum term of four years. Our articles of association provide that the Management Board members must retire periodically in accordance with a rotation schedule adopted by the Management Board. A Management Board member who retires in accordance with the rotation schedule may be reappointed immediately for a term of not more than four years at a time.

In view of the resignation of Mr Beukema a new succession plan for Management Board members will be established by the Supervisory Board in 2019 that is aimed at retaining the requisite expertise, experience and diversity.

**Supervisory Board**

Our Supervisory Board is responsible for the supervision of the activities of our Management Board and our Company's general affairs and business. Our Supervisory Board may, also on its own initiative, provide the Management Board with advice and may request any information from the Management Board that it deems appropriate. In performing its duties, the Supervisory Board is required to act in the interests of our Company (including its stakeholders) and its associated business as a whole. The members of the Supervisory Board are not authorized to represent us in dealings with third parties.

Pursuant to Dutch law, members of the Supervisory Board must be natural persons. Under our articles of association, the number of Supervisory Board members is determined by our Supervisory Board itself, provided there will be at least three Supervisory Board members. Our articles of association provide that members of the Supervisory Board are appointed by the general meeting of shareholders upon a binding nomination by the Supervisory Board. Our general meeting of shareholders may at all times deprive such a nomination of its binding character by a resolution passed by at least two-thirds of the votes cast

representing more than 50% of our issued share capital, following which our Supervisory Board shall draw up a new binding nomination.

Our Supervisory Board rules provide that members of our Supervisory Board will serve for a maximum duration of three terms of four years. Our articles of association provide that the Supervisory Board members must retire periodically in accordance with a rotation schedule adopted by the Supervisory Board. A Supervisory Board member who retires in accordance with the rotation schedule can be reappointed immediately. The Supervisory Board appoints a chairman from among its members.

With the exception of Dinko Valerio and Antoine Papiernik, each member of our Supervisory Board has been and remains fully independent within the meaning of best practice provision 2.1.8 of the DCGC. Mr. Dinko Valerio has provided a convertible loan to Amylon Therapeutics B.V. This loan becomes payable on demand after 24 months in equal quarterly terms. Mr. Papiernik is affiliated with Sofinnova which holds 7.1% of our shares. Both are therefore not independent within the meaning of best practice provision 2.1.8 of the Code. We feel their membership of the supervisory board is justified by their specific knowledge and experience of our business. Moreover, we do comply with best practice provision 2.1.7 of the DCGC, as only two out of 5 supervisory board members are not independent under best practice provision 2.1.8 of the Code and they are so under different criteria of said provision 2.1.8.

Under our articles of association, the general meeting of shareholders may suspend or remove Supervisory Board members at any time. A resolution of our general meeting of shareholders to suspend or remove a Supervisory Board member may be passed by a simple majority of the votes cast, provided that the resolution is based on a proposal by our Supervisory Board. In the absence of a proposal by our Supervisory Board, a resolution of our general meeting of shareholders to suspend or remove a Supervisory Board member shall require a majority of at least two-thirds of the votes cast representing more than 50% of our issued share capital.

In a meeting of the Supervisory Board, each Supervisory Board member is entitled to cast one vote. A Supervisory Board member may grant a written proxy to another Supervisory Board member to represent him at a meeting of the Supervisory Board. All resolutions by our Supervisory Board are adopted by a simple majority of the votes cast unless our Supervisory Board rules provide otherwise. In case of a tie in any vote of the Supervisory Board, the chairman of the Supervisory Board shall have the casting vote. Our Supervisory Board may also adopt resolutions outside a meeting, provided that such resolutions are adopted in writing, all Supervisory Board members are familiar with the resolution to be passed and provided that no Supervisory Board member objects to such decision-making process.

A succession plan for Supervisory Board members is in place that is aimed at retaining the balance in the requisite expertise, experience and diversity.

**Committees of the Supervisory Board**

We have an audit committee, a compensation committee and a nominating and corporate governance committee. We have adopted a charter for each of these committees.

***Audit Committee***

Our audit committee consists of Paul Baart (chairman), Alison Lawton and James Shannon. Each member satisfies the independence requirements of the NASDAQ listing standards / Rule 10A-3(b)(1) under the Exchange Act, and each member meets the criteria for independence set forth in best practice 2.1.8 of the DCGC. Paul Baart qualifies as an “audit committee financial expert,” as defined by the SEC in Item 16A: “Audit Committee Financial Expert” and as determined by our Supervisory Board. The audit committee oversees our

accounting and financial reporting processes and the audits of our financial statements. The audit committee is responsible for, among other things:

- the operation of the internal risk management and control systems, including supervision of the enforcement of relevant primary and secondary legislation, and supervising the operation of codes of conduct;
- the provision of financial information by the company (choice of accounting policies, application and assessment of the effects of new rules, information about the handling of estimated items in the financial statements, forecasts, work of internal and external auditors, etc.);
- compliance with recommendations and observations of internal and external auditors;
- the policy of the company on tax planning;
- relations with the external auditor, including, in particular, his independence, remuneration and any non-audit services for the company;
- the financing of the company; and
- the applications of information and communication technology, including risks relating to cyber security;
- annually reviewing the need for an internal audit function:
  the Supervisory Board has decided not to create an internal audit function for the time being, since the current scope of the business does not justify such a fulltime role. The Supervisory Board has delegated an active role to its Audit Committee in the design, implementation and monitoring of internal risk management and control system to manage the significant risks to which the Company is exposed.

***Compensation Committee***

Our compensation committee consists of James Shannon (chairman), Dinko Valerio and Alison Lawton. Each member satisfies the independence requirements of the NASDAQ listing standards / Rule 10A-3(b)(1) under the Exchange Act, and each member meets the criteria for independence set forth in best practice 2.1.8 of the DCGC, with the exception of Dinko Valerio, as set forth above. The compensation committee assists our Supervisory Board in reviewing and approving or recommending our compensation structure, including all forms of compensation relating to our Supervisory Board members, our Management Board members and our officers. Members of our Management Board may not be present at any compensation committee meeting while their compensation is deliberated. Subject to and in accordance with the terms of the compensation policy approved by our general meeting of shareholders from time to time, as required by Dutch law, the compensation committee is responsible for, among other things:

- making a proposal to the Supervisory Board for the remuneration policy to be pursued;
- making a proposal for the remuneration of the individual members of the Management Board, for adoption by the Supervisory Board; such proposal shall, in any event, deal with: (i) the remuneration structure and (ii) the amount of the fixed remuneration, the shares and/or options to be granted and/or other variable remuneration components, pension rights, redundancy pay and other forms of compensation to be awarded, as well as the performance criteria and their application; and
- preparing the remuneration report as referred to in best practice provision 3.4.1.

Our Supervisory Board may also delegate certain tasks and powers under our Option Plan to the compensation committee.

***Nominating and Corporate Governance Committee***

Our nominating and corporate governance committee consists of Dinko Valerio (chairman) and Paul Baart. Each member satisfies the independence requirements of the NASDAQ listing standards and Paul Baart satisfies the criteria for independence set forth in best practice 2.1.8 of the DCGC. The nominating and corporate governance committee assists our Supervisory Board in selecting individuals qualified to become our Supervisory Board members and Management Board members and in determining the composition of

the Management Board, Supervisory Board and its committees and our officers. The nominating and corporate governance committee is responsible for, among other things:

- drawing up selection criteria and appointment procedures for Supervisory Board members and Management Board members;
- periodically assessing the size and composition of the Supervisory Board and the Management Board, and making a proposal for a composition profile of the Supervisory Board;
- periodically assessing the functioning of individual Supervisory Board members and Management Board members, and reporting on this to the Supervisory Board;
- making proposals for appointments and reappointments; and
- supervising the policy of the Management Board on the selection criteria and appointment procedures for senior management.

**Insurance and Indemnification of Management Board and Supervisory Board Members**
Under Dutch law, Management Board members, Supervisory Board members and certain other representatives may be held liable for damages in the event of improper or negligent performance of their duties. They may be held jointly and severally liable for damages to the Company for infringement of the articles of association or of certain provisions of the Dutch Civil Code. They may also be liable towards third parties for infringement of certain provisions of the Dutch Civil Code. In certain circumstances they may also incur additional specific civil and criminal liabilities.

Our articles of association provide that we will indemnify our Management Board members, Supervisory Board members, former Management Board members and former Supervisory Board members (each an "Indemnified Person") against (i) any financial losses or damages incurred by such Indemnified Person and (ii) any expense reasonably paid or incurred by such Indemnified Person in connection with any threatened, pending or completed suit, claim, action or legal proceedings, whether civil, criminal, administrative or investigative and whether formal or informal, in which he becomes involved, to the extent this relates to his position with the Company, in each case to the fullest extent permitted by applicable law. No indemnification shall be given to an Indemnified Person (a) if a Dutch court has established, without possibility for appeal, that the acts or omissions of such Indemnified Person that led to the financial losses, damages, suit, claim, action or legal proceedings result from either an improper performance of his duties as an officer of the Company or an unlawful or illegal act and (b) to the extent that his financial losses, damages and expenses are covered by an insurance and the insurer has settled these financial losses, damages and expenses (or has indicated that it would do so). Our Supervisory Board may stipulate additional terms, conditions and restrictions in relation to such indemnification.

**Board composition and diversity**
Our Management Board comprised two persons in 2018, both of whom are male. Our Supervisory Board has four male members and one female member. As a Company, we support diversity of culture, gender and age in our Company. ProQR maintains a culture that reflects that ProQR is a multicultural company representing employees from over twenty countries. The culture is represented by the commitment to conducting our business ethically and to observing applicable laws, rules and regulations. In this context the Code of Conduct and Whistleblower policy are implemented and strongly anchored in the organization. Effectiveness of the Code of Conduct is monitored periodically.

Our current Management Board and Supervisory Board members were selected based on the required profile and talent and abilities of the members without positive or negative bias on gender, culture or age. In the future, this will continue to be our basis for selection of new Board members.

**General Meeting of Shareholders**

General meetings of shareholders may be held in Leiden, Oegstgeest, Leidschendam, Katwijk, Noordwijk, Wassenaar, Amsterdam, Rotterdam, The Hague, or Schiphol Airport (municipality of Haarlemmermeer), the Netherlands. All shareholders and others entitled to attend general meetings of shareholders are authorized to attend the general meeting of shareholders, to address the meeting and, in so far as they have such right, to vote, either in person or by proxy.

Annually, at least one general meeting of shareholders shall be held, within six months after the end of our financial year. A general meeting of shareholders shall also be held within three months after our Management Board has considered it to be likely that the Company's equity has decreased to an amount equal to or lower than half of its paid up and called up capital. If the Management Board and Supervisory Board have failed to ensure that such general meetings of shareholders as referred to in the preceding sentences are held in a timely fashion, each shareholder and other person entitled to attend shareholders' meetings may be authorized by the Dutch court to convene the general meeting of shareholders.

Our Management Board and our Supervisory Board may convene additional extraordinary general meetings of shareholders whenever they so decide. Pursuant to Dutch law, one or more shareholders and/or others entitled to attend general meetings of shareholders, alone or jointly representing at least ten percent of our issued share capital may on their application, be authorized by the Dutch court to convene a general meeting of shareholders. The Dutch court will disallow the application if it does not appear to it that the applicants have previously requested that the Management Board or Supervisory Board convenes a shareholders' meeting and neither the Management Board nor the Supervisory Board has taken the necessary steps so that the shareholders' meeting could be held within six weeks after the request.

General meetings of shareholders are convened by a notice which includes an agenda stating the items to be discussed. For the annual general meeting of shareholders the agenda will include, among other things, the adoption of our annual accounts, the appropriation of our profits or losses, discharge of the members of the Management Board for their management, discharge of the members of the Supervisory Board for their supervision on the management and proposals relating to the composition and filling of any vacancies of the Management Board or Supervisory Board. In addition, the agenda for a general meeting of shareholders includes such items as have been included therein by our Management Board or our Supervisory Board. Pursuant to Dutch law, one or more shareholders and/or others entitled to attend general meetings of shareholders, alone or jointly representing at least 3% of the issued share capital have the right to request the inclusion of additional items on the agenda of shareholders' meetings. Such requests must be made in writing, substantiated, or by a proposal for a resolution and received by us no later than the sixtieth day before the day the relevant general meeting is held. No resolutions will be adopted on items other than those which have been included in the agenda.

We will give notice of each general meeting of shareholders by publication on our website and, to the extent required by applicable law, in a Dutch daily newspaper with national distribution, and in any other manner that we may be required to follow in order to comply with Dutch law, applicable stock exchange and SEC requirements. We will observe the statutory minimum convening notice period for a general meeting of shareholders.

Pursuant to our articles of association, our Management Board may determine a record date ("registratiedatum") of 28 calendar days prior to a general meeting of shareholders to establish which shareholders and others with meeting rights are entitled to attend and, if applicable, vote in the general meeting of shareholders. The record date, if any, and the manner in which shareholders can register and exercise their rights will be set out in the convocation notice of the general meeting. Our articles of association provide that a shareholder must notify the Company in writing of his identity and his intention to

attend (or be represented at) the general meeting of shareholders, such notice to be received by us ultimately on the seventh day prior to the general meeting. If this requirement is not complied with or if upon direction of the Company to that effect no proper identification is provided by any person wishing to enter the general meeting of shareholders, the chairman of the general meeting of shareholders may, in his sole discretion, refuse entry to the shareholder or his proxy holder.

Pursuant to our articles of association, our general meeting of shareholders is chaired by the chairman of our Supervisory Board. If the chairman of our Supervisory Board is absent and has not charged another person to chair the meeting in his place, the Supervisory Board members present at the meeting shall appoint one of them to be chairman. If no Supervisory Board members are present at the general meeting of shareholders, the general meeting of shareholders will be chaired by our CEO or, if our CEO is absent, another Managing Board member present at the meeting and, if none of them is present, the general meeting shall appoint its own chairman. The person who should chair the meeting may appoint another person in his stead.

The chairman of the general meeting may decide at his discretion to admit other persons to the meeting. The chairman of the general meeting shall appoint another person present at the shareholders' meeting to act as secretary and to minute the proceedings at the meeting. The chairman of the general meeting may instruct a civil law notary to draw up a notarial report of the proceedings at the Company's expense, in which case no minutes need to be taken. The chairman of the general meeting is authorized to eject any person from the general meeting of shareholders if the chairman considers that person to disrupt the orderly proceedings. The general meeting of shareholders shall be conducted in the English language.

***Voting Rights and Quorum Requirements***

In accordance with Dutch law and our articles of association, each issued ordinary share and preferred share confers the right on the holder thereof to cast one vote at the general meeting of shareholders. The voting rights attached to any shares held by us or our direct or indirect subsidiaries are suspended as long as they are held in treasury. Dutch law does not permit cumulative voting for the election of Management Board members or Supervisory Board members.

Voting rights may be exercised by shareholders or by a duly appointed proxy holder (the written proxy being acceptable to the chairman of the general meeting of shareholders) of a shareholder, which proxy holder need not be a shareholder. Our articles of association do not limit the number of shares that may be voted by a single shareholder.

Under our articles of association, blank votes, abstentions and invalid votes shall not be counted as votes cast. Further, shares in respect of which a blank or invalid vote has been cast and shares in respect of which the person with meeting rights who is present or represented at the meeting has abstained from voting are counted when determining the part of the issued share capital that is present or represented at a general meeting of shareholders. The chairman of the general meeting shall determine the manner of voting and whether voting may take place by acclamation.

In accordance with Dutch law and generally accepted business practices, our articles of association do not provide quorum requirements generally applicable to general meetings of shareholders. To this extent, our practice varies from the requirement of NASDAQ Listing Rule 5620(c), which requires an issuer to provide in its bylaws for a generally applicable quorum, and that such quorum may not be less than one-third of the outstanding voting shares.

Resolutions of the general meeting of shareholders are adopted by a simple majority of votes cast without quorum requirement, except where Dutch law or our articles of association provide for a special majority and/or quorum in relation to specified resolutions.

**Anti-takeover provisions**

We have adopted several provisions that may have the effect of making a takeover of our Company more difficult or less attractive, including:

- granting a perpetual and repeatedly exercisable call option to a protection foundation, which confers upon the protection foundation the right to acquire, under certain conditions, the number of preferred shares in the capital of the Company. The issuance of such preferred shares will occur upon the protection foundation's exercise of the call option and will not require shareholder consent;
- the staggered four-year terms of our Supervisory Board members, as a result of which only approximately one-fourth of our Supervisory Board members will be subject to election in any one year;
- a provision that our Management Board members and Supervisory Board members may only be appointed upon a binding nomination by our Supervisory Board, which can be set aside by a two-thirds majority of our shareholders representing more than half of our issued share capital;
- a provision that our Management Board members and Supervisory Board members may only be removed by our general meeting of shareholders by a two-thirds majority of votes cast representing more than 50% of our issued share capital (unless the removal was proposed by the Supervisory Board); and
- a requirement that certain matters, including an amendment of our articles of association, may only be brought to our shareholders for a vote upon a proposal by our Management Board that has been approved by our Supervisory Board.

**Deviations from the Dutch Corporate Governance Code**

The Code contains a "comply-or-explain" principle, offering the possibility to deviate from the Code as long as any such deviations are explained. We acknowledge the importance of good corporate governance. However, at this stage, we do not comply with all the provisions of the DCGC for specific reasons. The main deviations from best practice provisions are listed below.

- Pursuant to the best practice provisions 3.1.2.vi and 3.1.2.vii of the DCGC, options granted to our Management Board members should not be exercisable during the first three years after the date of grant; shares granted to our Management Board members for no financial consideration should be retained by them for a period of at least five years or until they cease to hold office, whichever is the shorter period; and the number of options and/or shares granted to our management Board members should be dependent on the achievement of pre-determined performance criteria. We do not intend to comply with all of the above requirements as we believe it is in the best interest of the company to attract and retain highly skilled Management Board members on conditions based on market competitiveness.
- Pursuant to best practice provision 3.2.3 the remuneration of the Management Board in the event of dismissal may not exceed one year's salary. The management services agreements with our Management Board members provide for a lump-sum equal to 24 months of the individual's monthly gross fixed salary. Based on the risk profile of the Company and to be able to attract highly skilled management, we assumed this period to be appropriate.
- Best practice provision 3.3.2 prohibits the granting of shares or rights to shares to members of the Supervisory Board as compensation. It is common practice for companies listed on the NASDAQ Global Market to grant shares to the members of the Supervisory Board as compensation, in order to align the interests of the members of the Supervisory Board with our interests and those of our shareholders, and we have granted and expect to grant options to acquire ordinary shares to some of our Supervisory Board members.
- Pursuant to best practice provision 3.3.3, any shares held by Supervisory Board members are long-term investments. We do not request our Supervisory Board members to comply with this provision. We

believe it is in the best interest of the Company not to apply this provision in order to be able to attract and retain highly skilled Supervisory Board members on internationally competitive terms.

- Best practice provision 4.3.3 provides that the general meeting of shareholders may pass a resolution to cancel the binding nature of a nomination for the appointment of a member of the Management Board or of the Supervisory Board or a resolution to dismiss such member by an absolute majority of the votes cast. It may be provided that such majority should represent a given proportion of the issued capital, but this proportion may not exceed one third. In addition, best practice 4.3.3 provides that if such proportion of the share capital is not represented at the meeting, but an absolute majority of the votes cast is in favor of a resolution to cancel the binding nature of the nomination, a new general meeting of shareholders will be convened where the resolution may be adopted by absolute majority, regardless of the proportion of the share capital represented at the meeting. Our articles of association provide that these resolutions can only be adopted with at least a 2/3 majority which must represent more than 50% of our issued capital, and that no such second meeting will be convened, because we believe that the decision to overrule a nomination by the Management Board or the Supervisory Board for the appointment or dismissal of a member of our Management Board or of our Supervisory Board must be widely supported by our shareholders.
- Best practice provision 4.2.3 stipulates that meetings with analysts, presentations to analysts, presentations to investors and institutional investors and press conferences must be announced in advance on the Company's website and by means of press releases. Provision must be made for all shareholders to follow these meetings and presentations in real time, for example by means of webcasting or telephone. After the meetings, the presentations must be posted on the Company's website. We believe that enabling shareholders to follow in real time all the meetings with analysts, presentations to analysts and presentations to investors, would create an excessive burden on our resources and therefore, we do not intend to comply with all of the above requirements.
- Best practice provision 4.2.2 stipulates that an outline policy on bilateral contacts with the shareholders shall be formulated and published on the Company's website. The Company has not formulated such policy as it believes this is already covered by our regular process for public disclosure of information.

**Summary of significant corporate governance differences from NASDAQ Listing Standards**

Our ordinary shares are listed on NASDAQ. The Sarbanes-Oxley Act of 2002, as well as related rules subsequently implemented by the SEC, requires foreign private issuers, including our Company, to comply with various corporate governance practices. As a foreign private issuer, subject to certain exceptions, the NASDAQ listing standards permit a foreign private issuer to follow its home country practice in lieu of the NASDAQ listing standards. Our corporate governance practices differ in certain respects from those that U.S. companies must adopt in order to maintain a NASDAQ listing. The home country practices followed by our Company in lieu of NASDAQ rules are described below:

- We do not intend to follow NASDAQ's quorum requirements applicable to meetings of shareholders. In accordance with Dutch law and generally accepted business practice, our articles of association do not provide quorum requirements generally applicable to general meetings of shareholders.
- We do not intend to follow NASDAQ's requirements regarding the provision of proxy statements for general meetings of shareholders. Dutch law does not have a regulatory regime for the solicitation of proxies and the solicitation of proxies is not a generally accepted business practice in the Netherlands. We do intend to provide shareholders with an agenda and other relevant documents for the general meeting of shareholders and shareholders will be entitled to give proxies and voting instructions to us and/or third parties.

We intend to take all actions necessary for us to maintain compliance as a foreign private issuer under the applicable corporate governance requirements of the Sarbanes-Oxley Act of 2002, the rules adopted by the SEC and NASDAQ's listing standards.

**Controls and procedures**

In accordance with the Dutch Corporate Governance Code, we have assessed the design and operational effectiveness of our Risk & Control framework. Based on the activities performed during 2018, and in accordance with provision 1.4.3, the Management Board considers that:

- this report provides sufficient insights into any failings in the effectiveness of the internal risk management and control systems;
- the aforementioned systems provide reasonable assurance that the financial reporting does not contain any material inaccuracies;
- based on the current state of affairs, it is justified that the financial reporting is prepared on a going concern basis; and
- the report states those material risks and uncertainties that are relevant to the expectation of the company's continuity for the period of twelve months after the preparation of this report.

In accordance with the Dutch Financial Supervision Act, section 5.25c, the Management Board declares that, to the best of its knowledge:

- the financial statements for 2018 provide, in accordance with IFRS as endorsed by the EU, a true and fair view of the consolidated assets, liabilities and financial position as at December 31, 2018, and of the 2018 consolidated income statement of ProQR Therapeutics N.V.;
- the annual report provides a true and fair view of the situation as at December 31, 2018, and the state of affairs during the financial year 2018, together with a description of the principal risks faced by the Group

# Risk Management

Our business is subject to numerous risks and uncertainties. In the table below, we focus on the key risks and uncertainties the Company currently faces. For the avoidance of doubt, this does not mean that the risks which were previously signaled and not described here are no longer relevant. For a complete understanding of the risks that we face you should also read the full list of risks and uncertainties as disclosed in item 3.D Risk Factors of the annual report on Form 20-F. Some of these risks and uncertainties are outside the control of the Company, others may be influenced or mitigated. In 2015, we have implemented a Risk & Control framework, based on the COSO 2013 internal control framework, for enhancing our control environment as well as compliance with the U.S. SEC's Sarbanes Oxley (SOx) Act of 2002, which we are required to do as a company listed on the NASDAQ. As part of the SOx implementation program, our Risk & Control framework was further enhanced in 2018, focusing on IT and entity level controls. Improvement of our Risk & Control framework is an ongoing effort for the Company.

We have defined our risk tolerance on a number of internal and external factors including:

- Financial strength in the long run;
- Liquidity in the short run;
- Business performance measures;
- Scientific risks and opportunities;
- Compliance with relevant rules and regulations;
- Reputation.

The identification and analysis of risks is an ongoing process that is naturally a critical component of internal control. On the basis of these factors and ProQR's risk tolerance, improvement of our Risk & Control framework and monitoring of the risks is an ongoing effort for the Company.

Our main risks are those that threaten the achievement of the Company's corporate objectives, including compliance. If any of these risks actually occurs, our business, prospects, operating results and financial condition could suffer materially. These risks include, but are not limited to, the following:

| Risk related to | Risk area | Expected impact upon materialization | Risk appetite / risk-mitigating actions |
|---|---|---|---|
| **Development and Regulatory Approval of our Product Candidates** | Our products might not be able to demonstrate safety and efficacy in the preclinical studies and clinical trials that are needed to obtain product approval. | The Company would be unable to commercialize the products and therefore generate revenues. | This is an inherent risk with drug development as the safety and efficacy of products can only be assessed when these studies are conducted. However, the Company has multiple products in the pipeline and therefore is diversified. The Company also monitors the progress of the programs and aims to make decisions that mitigate safety and efficacy related risks. |

| Risk related to | Risk area | Expected impact upon materialization | Risk-mitigating actions |
|---|---|---|---|
| | The regulatory approval process is lengthy, time-consuming and unpredictable and products developed may ultimately not lead to regulatory approval of the product. | Failure to comply with the requirements in the regulatory process could result in delays, suspension, refusals and withdrawal of approvals as well as fines. | Although the Company monitors the regulatory landscape and engages with the authorities when it deems that necessary, this is an inherent risk in biotech drug development and therefore has limited mitigation abilities. |
| | We may not able to maintain orphan product status for eluforsen, sepofarsen (formerly: QR-110), QR-411 and QR-421a or obtain such status for any other product canditates. | We may not benefit from rewards including fee reductions and market exclusivity. Sales could be impacted if other products are granted authorization for the same indications as eluforsen, sepofarsen, QR-411 and QR-421a. | We take orphan drug requirements into consideration in the design of our clinical development plans. |
| | We may be precluded from obtaining marketing authorization for our products when our competitors have obtained market exclusivity before we do. | We may encounter delays in marketing our products for a significant period of time. | We take orphan drug requirements into consideration in the design of our clinical development plans. |
| **Capital Needs and Financial Position** | The Company depends largely on equity financing and financing through third party collaboration agreements and government subsidies. | Volatility of the Company's share price, failure to deliver under collaboration agreements and/or the reevaluation or withdrawal of government subsidies may have a negative impact on the Company's ability to obtain future financing. | The ability of third party financing is dependent on external factors and is therefore not entirely in the Company's control. The Company monitors the market conditions for opportunities to add additional capital. |
| **Dependence on Third Parties** | The Company relies upon third-party contractors and service providers for the execution of several aspects of its preclinical and clinical development programs, which include CRO's, third party manufacturers and other service providers. | Failure of third parties to provide services of a suitable quality and within acceptable timeframes may cause delay or failure of the Company's development programs. | The Company reviews and monitors the activities of the third parties. These include setting contractual deliverables, quality assurance audits and performance reports, among other activities. |
| **Intellectual Property** | The Company is highly dependent on its portfolio of patents and other intellectual property, proprietary information and knowhow and its ability to protect and enforce these assets.<br><br>The Company is subject to the risk of infringing third party intellectual property rights. | Inadequate intellectual property protection or enforcement may impede the Company's ability to compete effectively. If the Company is not able to protect its trade secrets, know-how or other proprietary information, the value of its technology and product candidates could be significantly diminished. Intellectual property rights conflicts may result in costly litigation and could result in the Company having to pay substantial damages or limit the Company's ability to commercialize its product candidates. | The Company files and prosecutes patent applications to protect its products and technologies to the best of its knowledge and with assistance from internal and external counsel. Prior to disclosing any confidential information to third parties, the Company maintains strict confidentiality standards and agreements for collaborating parties. |

| Risk related to | Risk area | Expected impact upon materialization | Risk-mitigating actions |
|---|---|---|---|
| **Commercialization of Our Product Candidates** | We face competition from entities that have developed or may develop product candidates for our target indications. | If our competitors develop technologies or product candidates more rapidly than we do or their technologies, including delivery technologies, are more effective, our ability to develop and successfully commercialize our product candidates may be adversely affected. | Competition is an inherent risk for any industry including drug development. Through our IP strategy and orphan drug designation application, we attempt to have data exclusivity for our products. Development in other companies is essentially out of our control but we monitor the competitive landscape and incorporate that into our business strategy. |
| **Reimbursement from third-party payors** | The availability of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates, if approved, will depend substantially on the extent to which the costs of these product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. | If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize any product candidate. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment. | The ability of third party financing is dependent on external factors and is therefore not entirely in the Company's control. The Company monitors the market conditions for opportunities to seek reimbursement. |

The above risks have not materialized in 2018. In addition to the above key risks, the Company's activities expose it to a variety of financial risks: market risk (including currency risk, interest rate risk and price risk), credit risk and liquidity risk. Unfavorable exchange rate developments and historically low interest rates may impact the financial income of the Company. The Company has a cash management policy in place to minimize potential adverse effects resulting from unpredictability of financial markets on the Company's financial performance.

# Financial Statements 2018

## Consolidated statement of financial position at December 31, 2018

| | Note | December 31, 2018 | December 31, 2017 |
|---|---|---|---|
| | | *€ 1,000* | *€ 1,000* |
| **ASSETS** | | | |
| **Non-current assets** | | | |
| Intangible assets | 7 | -- | 39 |
| Property, plant and equipment | 8 | 1,864 | 2,505 |
| | | **1,864** | **2,544** |
| **Current assets** | | | |
| Social securities and other taxes | 9 | 1,243 | 396 |
| Prepayments and other receivables | 10 | 1,544 | 2,064 |
| Cash and cash equivalents | 11 | 105,580 | 48,099 |
| | | **108,367** | **50,559** |
| | | | |
| **TOTAL ASSETS** | | **110,231** | **53,103** |
| | | | |
| **EQUITY** | | | |
| Share capital | | 1,726 | 1,457 |
| Share premium | | 235,744 | 148,763 |
| Reserves | | 10,888 | 8,513 |
| Accumulated deficit | | (155,443) | (119,370) |
| **Equity attributable to owners of the Company** | | **92,915** | **39,363** |
| Non-controlling interests | | (230) | (38) |
| **TOTAL EQUITY** | **12** | **92,685** | **39,325** |
| | | | |
| **LIABILITIES** | | | |
| **Non-current liabilities** | | | |
| Borrowings | | 9,386 | 5,284 |
| | **13** | **9,386** | **5,284** |
| **Current liabilities** | | | |
| Borrowings | | -- | 1,960 |
| Trade payables | | 135 | 546 |
| Social securities and other taxes | | -- | 1,019 |
| Pension premiums | | 7 | -- |
| Deferred income | | 545 | 347 |
| Other current liabilities | | 7,473 | 4,622 |
| | **14** | **8,160** | **8,494** |
| | | | |
| **TOTAL LIABILITIES** | | **17,546** | **13,778** |
| | | | |
| **TOTAL EQUITY AND LIABILITIES** | | **110,231** | **53,103** |

The accompanying notes are an integral part of these financial statements.

# Consolidated statement of profit or loss and comprehensive income for the year ended December 31, 2018

| | Note | 2018 | 2017 |
|---|---|---|---|
| | | *€ 1,000* | *€ 1,000* |
| **Other income** | **15** | **5,761** | **1,495** |
| Research and development costs | 16 | (29,514) | (31,153) |
| General and administrative costs | | (12,540) | (10,840) |
| **Total operating costs** | | **(42,054)** | **(41,993)** |
| **Operating result** | | **(36,293)** | **(40,498)** |
| Financial income and expense | 18 | (792) | (3,175) |
| **Result before corporate income taxes** | | **(37,085)** | **(43,673)** |
| Corporate income taxes | 19 | (1) | (2) |
| **Result for the year** | | **(37,086)** | **(43,675)** |
| **Other comprehensive income** | | | |
| *Items that will never be reclassified to profit or loss* | | | |
| *Items that are or may be reclassified to profit or loss* | | | |
| Foreign operations – foreign currency translation differences | | (28) | 151 |
| **Total comprehensive income for the year (attributable to equity holders of the Company)** | | **(37,114)** | **(43,524)** |
| **Result attributable to** | | | |
| Owners of the Company | | (36,894) | (43,637) |
| Non-controlling interests | | (192) | (38) |
| | | **(37,086)** | **(43,675)** |
| **Share information** | 20 | | |
| Weighted average number of shares outstanding[1] | | 34,052,520 | 25,374,807 |
| **Earnings per share attributable to the equity holders of the Company (expressed in Euro per share)** | | | |
| Basic earnings per share[1] | | (1.08) | (1.72) |
| Diluted earnings per share[1] | | (1.08) | (1.72) |

*The accompanying notes are an integral part of these financial statements.*

[1] Basic and diluted earnings are equal due to the anti-dilutive nature of the options outstanding since the Company is loss-making.

## Consolidated statement of changes in equity for the year ended December 31, 2018

| | Attributable to owners of the Company | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Share Capital | Share Premium | Equity Settled Employee Benefit Reserve | Translation Reserve | Accumulated Deficit | Total | Non-controlling Interests | Total Equity |
| | € 1,000 | € 1,000 | € 1,000 | € 1,000 | € 1,000 | € 1,000 | € 1,000 | € 1,000 |
| **Balance at January 1, 2017** | **934** | **123,597** | **4,353** | **(15)** | **(75,733)** | **53,136** | **--** | **53,136** |
| Result for the year | -- | -- | -- | -- | (43,637) | (43,637) | (38) | (43,675) |
| Other comprehensive income | -- | -- | -- | 151 | -- | 151 | -- | 151 |
| Recognition of share-based payments | -- | -- | 4,024 | -- | -- | 4,024 | -- | 4,024 |
| Issue of ordinary shares | 343 | 25,342 | -- | -- | -- | 25,685 | -- | 25,685 |
| Issue of treasury shares | 180 | (180) | -- | -- | -- | 0 | -- | 0 |
| Share options exercised | 0 | 4 | -- | -- | -- | 4 | -- | 4 |
| **Balance at December 31, 2017** | **1,457** | **148,763** | **8,377** | **136** | **(119,370)** | **39,363** | **(38)** | **39,325** |
| Result for the year | -- | -- | -- | -- | (36,984) | (36,894) | (192) | (37,086) |
| Other comprehensive income | -- | -- | -- | (28) | -- | (28) | -- | (28) |
| Recognition of share-based payments | 4 | 2,185 | 3,224 | -- | -- | 5,413 | -- | 5,413 |
| Issue of ordinary shares | 265 | 83,926 | -- | -- | -- | 84,191 | -- | 84,191 |
| Share options lapsed | -- | -- | (97) | -- | 97 | -- | -- | -- |
| Share options exercised | -- | 870 | (724) | -- | 724 | 870 | -- | 870 |
| **Balance at December 31, 2018** | **1,726** | **235,744** | **10,780** | **108** | **(155,443)** | **92,915** | **(230)** | **92,685** |

The accompanying notes are an integral part of these financial statements.

# Consolidated statement of cash flows for the year ended December 31, 2018

| | Note | 2018 | 2017 |
|---|---|---|---|
| | | *€ 1,000* | *€ 1,000* |
| **Cash flow from operating activities** | | | |
| Result for the year | | (37,086) | (43,675) |
| Adjustments for: | | | |
| — Amortization & depreciation | 7, 8 | 992 | 1,065 |
| — Share-based compensation | 12 | 5,413 | 4,024 |
| — Financial income and expense | 18 | 792 | 3,175 |
| — Net foreign exchange gain / (loss) | | (28) | 151 |
| | | | |
| Changes in working capital | | 1,295 | 164 |
| *Cash used in operations* | | *(28,622)* | *(35,096)* |
| | | | |
| Corporate income tax paid | | (1) | (2) |
| Interest received/(paid) | | 130 | 147 |
| | | | |
| ***Net cash used in operating activities*** | | ***(28,493)*** | ***(34,951)*** |
| | | | |
| **Cash flow from investing activities** | | | |
| Purchases of intangible assets | | -- | -- |
| Purchases of property, plant and equipment | | (312) | (121) |
| | | | |
| ***Net cash used in investing activities*** | | ***(312)*** | ***(121)*** |
| | | | |
| **Cash flow from financing activities** | | | |
| Proceeds from issuance of shares, net of transaction costs | | 84,191 | 25,685 |
| Proceeds from exercise of share options | | 870 | 4 |
| Proceeds from borrowings | 13 | 264 | 301 |
| Proceeds from convertible loans | 13 | 1,132 | 650 |
| Redemption of financial lease | 13 | -- | -- |
| | | | |
| ***Net cash generated by financing activities*** | | ***86,457*** | ***26,640*** |
| | | | |
| **Net increase/(decrease) in cash and cash equivalents** | | **57,652** | **(8,432)** |
| | | | |
| Currency effect cash and cash equivalents | | (171) | (2,669) |
| Cash and cash equivalents at the beginning of the year | 11 | 48,099 | 59,200 |
| | | | |
| **Cash and cash equivalents at the end of the year** | **11** | **105,580** | **48,099** |

The accompanying notes are an integral part of these financial statements.

# Notes to the consolidated financial statements for the year ended December 31, 2018

## 1. General Information

ProQR Therapeutics N.V., or "ProQR" or the "Company", is a development stage company domiciled in the Netherlands that primarily focuses on the development and commercialization of novel therapeutic medicines.

Since September 18, 2014, the Company's ordinary shares are listed on the NASDAQ Global Market under ticker symbol PRQR.

The Company was incorporated in the Netherlands, on February 21, 2012 (Chamber of Commerce no. 54600790) and was reorganized from a private company with limited liability to a public company with limited liability on September 23, 2014. The Company has its statutory seat in Leiden, the Netherlands. The address of its headquarters and registered office is Zernikedreef 9, 2333 CK Leiden, the Netherlands.

At December 31, 2018, ProQR Therapeutics N.V. is the ultimate parent company of the following entities:

- ProQR Therapeutics Holding B.V. (the Netherlands, 100%);
- ProQR Therapeutics I B.V. (the Netherlands, 100%);
- ProQR Therapeutics II B.V. (the Netherlands, 100%);
- ProQR Therapeutics III B.V. (the Netherlands, 100%);
- ProQR Therapeutics IV B.V. (the Netherlands, 100%);
- ProQR Therapeutics VI B.V. (the Netherlands, 100%);
- ProQR Therapeutics VII B.V. (the Netherlands, 100%);
- ProQR Therapeutics VIII B.V. (the Netherlands, 100%);
- ProQR Therapeutics IX B.V. (the Netherlands, 100%);
- ProQR Therapeutics I Inc. (United States, 100%);
- Amylon Therapeutics B.V. (the Netherlands, 80%);
- Amylon Therapeutics, Inc. (Unites States, a 100% subsidiary of Amylon Therapeutics B.V.)

ProQR Therapeutics N.V. is also statutory director of Stichting Bewaarneming Aandelen ProQR ("ESOP Foundation") and has full control over this entity.

As used in these consolidated financial statements, unless the context indicates otherwise, all references to "ProQR", the "Company" or the "Group" refer to ProQR Therapeutics N.V. including its subsidiaries and the ESOP Foundation.

## 2. Basis of preparation

### (a) Statement of compliance

These consolidated financial statements have been prepared in accordance with International Financial Reporting Standards, or IFRS, as adopted by the European Union ("EU").

With reference to the income statement of the Company, use has been made of the exemption pursuant to Section 402 of Book 2 of the Netherlands Civil Code.

### (b) Basis of measurement

The financial statements have been prepared on the historical cost basis except for financial instruments and share-based payment obligations which have been based on fair value. Historical cost is generally based on the fair value of the consideration given in exchange for assets.

## (c) Functional and presentation currency

These consolidated financial statements are presented in euro, which is the Company's functional currency. All amounts have been rounded to the nearest thousand, unless otherwise indicated.

## (d) Going Concern

The Management Board of ProQR has, upon preparing and finalizing the 2018 financial statements, assessed the Company's ability to fund its operations for a period of at least one year after the date of signing these financial statements.

The Management Board of the Company is confident about the continuity of the Company based on its existing funding, taking into account the Company's current cash position and the projected cash flows based on the activities under execution on the basis of ProQR's business plan and budget.

## (e) Use of estimates and judgements

In preparing these consolidated financial statements, management has made judgements, estimates and assumptions that affect the application of accounting policies and the reported amounts of assets, liabilities, income and expenses. Actual results may differ from these estimates.

Estimates and underlying assumptions are reviewed on an ongoing basis. Revisions to accounting estimates are recognized in the period in which the estimate is revised if the revision affects only that period or in the period of the revision and future periods if the revision affects both current and future periods.

Information about assumptions and estimation uncertainties that may have a significant risk of resulting in a material adjustment is included below.

**(i) Share-based payments**

Share options granted to employees and consultants are measured at the fair value of the equity instruments granted. Fair value is determined through the use of an option-pricing model considering, among others, the following variables:

- the exercise price of the option;
- the expected life of the option;
- the current value of the underlying shares;
- the expected volatility of the share price;
- the dividends expected on the shares; and
- the risk-free interest rate for the life of the option.

For the Company's share option plans, management's judgment is that the Black-Scholes valuation method is the most appropriate for determining the fair value of the Company's share options.

Initially, the Company's ordinary shares were not publicly traded and consequently the Company needed to estimate the fair value of its share and the expected volatility of that value. The expected volatility of all options granted was therefore based on the average historical volatility of the Company's peers over a period that agrees with the expected option life. All assumptions and estimates are further discussed in Note 12(d) to the financial statements. The value of the underlying shares was determined on the basis of the prior sale of company stock method. As such, the Company has benchmarked the value per share to external transactions of Company shares and external financing rounds.

For options granted from the moment of listing as stated above, the Company uses the closing price of the ordinary shares on the previous business day as exercise price of the options granted.

The result of the share option valuations and the related compensation expense is dependent on the model and input parameters used. Even though Management considers the fair values reasonable and defensible based on the methodologies applied and the information available, others might derive a different fair value for the Company's share options.

**(ii) Corporate income taxes**
The Company recognizes deferred tax assets arising from unused tax losses or tax credits only to the extent that the Company has sufficient taxable temporary differences or there is convincing evidence that sufficient taxable profit will be available against which the unused tax losses or unused tax credits can be utilized. Management's judgment is that such convincing evidence is currently not sufficiently available and a deferred tax asset is therefore only recognized to the extent that the Company has sufficient taxable temporary differences.

**(iii) Grant income**
(Government) Grant income is not recognized until there is reasonable assurance that the Company will comply with the conditions attached to them. (Government) Grants are recognized in profit or loss on a systematic basis over the period the Company recognizes as expenses the related costs for which the grants are expected to compensate.

**(iv) Research and development expenditures**
Research expenditures are currently not capitalized but are reflected in the income statement because the criteria for capitalization are not met. At each balance sheet date, the Company estimates the level of service performed by the vendors and the associated costs incurred for the services performed.

Although we do not expect the estimates to be materially different from amounts actually incurred, the understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in reporting amounts that are too high or too low in any particular period.

## (f) Changes in accounting policies

The financial statements have been prepared on the basis of International Financial Reporting Standards ("IFRS"), as issued by the International Accounting Standards Board ("IASB").

**IFRS 9**
IFRS 9 contains three principal classification categories for financial assets: measured at amortized cost, FVOCI and FVTPL. The classification of financial assets under IFRS 9 is generally based on the business model in which a financial asset is managed and its contractual cash flow characteristics. IFRS 9 eliminates the previous IAS 39 categories of held to maturity, loans and receivables and available for sale.

IFRS 9 largely retains the existing requirements in IAS 39 for the classification and measurement of financial liabilities. The adoption of IFRS 9 has not had a significant effect on the Group's accounting policies related to financial liabilities and derivative financial instruments.

Other new Standards and Interpretations, which became effective as of January 1, 2018, did not have a material impact on our financial statements.

## 3. Significant Accounting Policies

The Company has consistently applied the following accounting policies to all periods presented in these consolidated financial statements.

### (a) Basis of consolidation

**(i) Subsidiaries**

Subsidiaries are entities controlled by the Group. The Group controls an entity when it has power over the entity, is exposed to, or has rights to, variable returns from its involvement with the entity and has the ability to affect those returns through its power over the entity. The Group reassesses whether or not it controls an entity if facts and circumstances indicate that there are changes to one or more of these elements. The financial statements of subsidiaries are included in the consolidated financial statements from the date on which control commences until the date on which control ceases.

**(ii) Non-controlling interests ("NCI")**

NCI are measured at their proportionate share of the acquiree's identifiable net assets at the acquisition date. Changes in the Group's interest in a subsidiary that do not result in a loss of control are accounted for as equity transactions.

**(iii) Loss of control**

When the Group loses control over a subsidiary, it derecognizes the assets and liabilities of the subsidiary, and any non-controlling interests and other components of equity. Any resulting gain or loss is recognized in profit or loss. Any interest retained in the former subsidiary is measured at fair value when control is lost.

**(iv) Transactions eliminated on consolidation**

Intra-group balances and transactions, and any unrealized income and expenses arising from intra-group transactions, are eliminated. Unrealized gains arising from transactions with equity-accounted investees are eliminated against the investment to the extent of the Group's interest in the investee. Unrealized losses are eliminated in the same way as unrealized gains, but only to the extent that there is no evidence of impairment.

### (b) Classes of financial instruments

Financial instruments are both primary financial instruments, such as receivables and payables, and financial derivatives. For primary financial instruments, reference is made to the treatment per the corresponding balance sheet item.

Financial derivatives are valued at fair value. Upon first recognition, financial derivatives are recognized at fair value and then revalued as at balance sheet date.

### (c) Foreign currencies

**(i) Foreign currency transactions**

Foreign currency transactions are translated into the functional currency using the exchange rates prevailing at the dates of the transactions.

Monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rate at the reporting date. Non-monetary assets and liabilities denominated in foreign currencies that are measured at fair value are translated into the functional currency at the exchange rate when the fair value was determined. Foreign currency differences are generally recognized in profit or loss. Non-monetary items that are measured based on historical cost in a foreign currency are not translated.

**(ii) Foreign operations**

The assets and liabilities of foreign operations are translated into euro at exchange rates at the reporting date. The income and expenses of foreign operations are translated into euros at the exchange rates at the dates of the transactions. Foreign currency differences are recognized in OCI and accumulated in the translation reserve, except to the extent that the translation difference is allocated to NCI.

### (d) Recognition of other income

Other income includes amounts earned from third parties and are recognized when earned in accordance with the substance and under the terms of the related agreements and when it is probable that the economic benefits associated with the transaction will flow to the entity and the amount of the income can be measured reliably. The grants are recognized in other income on a systematic basis over the period the Company recognizes as expenses the related costs for which the grants are expected to compensate.

### (e) Government grants—WBSO

The WBSO ("afdrachtvermindering speur- en ontwikkelingswerk") is a Dutch fiscal facility that provides subsidies to companies, knowledge centers and self-employed people who perform research and development activities (as defined in the WBSO Act). Under this Act, a contribution is paid towards the labor costs of employees directly involved in research and development. The contribution is in the form of a reduction of payroll taxes and social security contributions recognized on a net basis within the labor costs. Subsidies relating to labor costs are deferred and recognized in the income statement in the period necessary to match them with the labor costs that they are intended to compensate.

### (f) Employee benefits

**(i) Short-term employee benefits**

Short-term employee benefits are expensed as the related service is provided. A liability is recognized for the amount expected to be paid if the Group has a present legal or constructive obligation to pay this amount as a result of past service provided by the employee and the obligation can be estimated reliably.

**(ii) Share-based payment transactions**

The grant-date fair value of equity-settled share-based payment awards granted to employees is generally recognized as an expense, with a corresponding increase in equity, over the vesting period of the awards. The amount recognized as an expense is adjusted to reflect the number of awards for which the related service and non-market performance conditions are expected to be met, such that the amount ultimately recognized is based on the number of awards that meet the related service conditions at the vesting date. For share-based payment awards with non-vesting conditions, the grant-date fair value of the share-based payment is measured to reflect such conditions and there is no true-up for differences between expected and actual outcomes.

**(iii) Pension obligations**

The Company operates defined contribution pension plans for all employees funded through payments to insurance companies. The Company has no legal or constructive obligation to pay further contributions once the contributions have been paid. The contributions are recognized as employee benefit expense when employees have rendered the service entitling them to the contributions. Prepaid contributions are recognized as an asset to the extent that a cash refund or a reduction in the future payments is available.

### (g) Taxation

Income tax expense represents the sum of the tax currently payable and deferred tax. It is recognized in profit or loss except to the extent that it relates to a business combination, or items recognized directly in equity or in OCI.

**(i) Current tax**
The tax currently payable is based on taxable profit for the year. Taxable profit differs from profit as reported in the income statement because of items of income or expense that are taxable or deductible in other years and items that are never taxable or deductible. The Company's liability for current tax is calculated using tax rates that have been enacted or substantively enacted by the end of the reporting period.

**(ii) Deferred tax**
Deferred tax is recognized on differences between the carrying amounts of assets and liabilities in the financial statements and the corresponding tax bases used in the computation of taxable profit.

The carrying amount of deferred tax assets is reviewed at the end of each reporting period and reduced to the extent that it is no longer probable that sufficient taxable profits will be available to allow all or part of the asset to be recovered. Since the Company does not expect to be profitable in the foreseeable future, its deferred tax assets are valued at nil.

Deferred tax assets and liabilities are measured at the tax rates that are expected to apply in the period in which the liability is settled or the asset realized, based on tax rates (and tax laws) that have been enacted or substantively enacted by the end of the reporting period. The measurement of deferred tax liabilities and assets reflects the tax consequences that would follow from the manner in which the Company expects, at the end of the reporting period, to recover or settle the carrying amount of its assets and liabilities.

## (h) Intangible assets

**(i) Licenses**
Acquired patents have a finite useful life and are carried at cost less accumulated amortization and impairment losses. Amortization is calculated using the straight-line method to allocate the cost of patents over their estimated useful lives (generally 10 years unless a patent expires prior to that date). Amortization begins when an asset is available for its intended use.

**(ii) Research and development**
Research expenditures are recognized as expenses as incurred. Costs incurred on development projects are recognized as intangible assets as of the date that it can be established that it is probable that future economic benefits that are attributable to the asset will flow to the Company considering its commercial and technological feasibility, generally when filed for regulatory approval for commercial production, and when costs can be measured reliably. Given the current stage of the development of the Company's products no development expenditures have yet been capitalized.

Registration costs for patents are part of the expenditures for the research and development project. Therefore, registration costs for patents are expensed as incurred as long as the research and development project concerned does not yet meet the criteria for capitalization.

**(iii) Other intangible assets**
Other intangible assets, including software, that are acquired by the Company and have finite useful lives are measured at cost less accumulated amortization and accumulated impairment losses.

**(iv) Amortization**
Amortization is calculated to write off the cost of intangible assets less their estimated residual values using the straight-line method over their estimated useful lives, and is recognized in profit or loss.

The estimated useful lives for current and comparative periods are as follows:

- software: 3 years.

Amortization methods, useful lives and residual values are reviewed at each reporting date and adjusted if appropriate.

## (i) Property, plant and equipment

**(i) Recognition and measurement**

Items of property, plant and equipment are measured at cost less accumulated depreciation and any accumulated impairment losses. If significant parts of an item of property, plant and equipment have different useful lives, then they are accounted for as separate items (major components) of property, plant and equipment. Any gain or loss on disposal of an item of property, plant and equipment is recognized in profit or loss.

**(ii) Depreciation**

Depreciation is calculated to write off the cost of items of property, plant and equipment less their estimated residual values using the straight-line method over their estimated useful lives, and is recognized in profit or loss. Leased assets are depreciated over the shorter of the lease term and their useful lives unless it is reasonably certain that the Company will obtain ownership by the end of the lease term.

The estimated useful lives of property, plant and equipment for current and comparative periods are as follows:

- leasehold improvements: 5 - 10 years;
- laboratory equipment: 5 years;
- other: 3 - 5 years.

Depreciation methods, useful lives and residual values are reviewed at each reporting date and adjusted if appropriate.

## (j) Impairment of tangible and intangible assets

At the end of each reporting period, the Company reviews the carrying amounts of its tangible and intangible assets to determine whether there is any indication that those assets have suffered an impairment loss. If any such indication exists, the recoverable amount of the asset is estimated in order to determine the extent of the impairment loss (if any). Where it is not possible to estimate the recoverable amount of an individual asset, the Company estimates the recoverable amount of the cash-generating unit to which the asset belongs. Where a reasonable and consistent basis of allocation can be identified, corporate assets are also allocated to individual cash-generating units, or otherwise they are allocated to the smallest group of cash-generating units for which a reasonable and consistent allocation basis can be identified.

Intangible assets with indefinite useful lives and intangible assets not yet available for use are tested for impairment at least annually, and whenever there is an indication that the asset may be impaired.

The recoverable amount is the higher of fair value less costs of disposal and value in use. In assessing value in use, the estimated future cash flows are discounted to their present value using a pre-tax discount rate that reflects current market assessments of the time value of money and the risks specific to the asset for which the estimates of future cash flows have not been adjusted.

If the recoverable amount of an asset (or cash-generating unit) is estimated to be less than its carrying amount, the carrying amount of the asset (or cash-generating unit) is reduced to its recoverable amount. An impairment loss is recognized immediately in profit or loss, unless the relevant asset is carried at a revalued amount, in which case the impairment loss is treated as a revaluation decrease.

Where an impairment loss subsequently reverses, the carrying amount of the asset (or cash-generating unit) is increased to the revised estimate of its recoverable amount, but so that the increased carrying amount does not exceed the carrying amount that would have been determined had no impairment loss been recognized for the asset (or cash-generating unit) in prior years. A reversal of an impairment loss is recognized immediately in profit or loss, unless the relevant asset is carried at a revalued amount, in which case the reversal of the impairment loss is treated as a revaluation increase.

## (k) Financial assets

All financial assets are recognized and derecognized on the trade date where the purchase or sale of a financial asset is under a contract whose terms require delivery of the financial asset within the timeframe established by the market concerned, and are initially measured at fair value and subsequently measured at amortized cost or fair value on the basis of the entity's business model for managing the financial assets and the contractual cash flow characteristics of the financial assets.

Specifically:

- debt instruments that are held within a business model whose objective is to collect the contractual cash flows, and that have contractual cash flows that are solely payments of principal and interest on the principal amount outstanding, are measured subsequently at amortised cost, and
- all other debt investments and equity investments are measured subsequently at fair value through profit or loss (FVTPL).

## (l) Contract receivables

Contract receivables, loans and other receivables that have fixed or determinable payments that are not quoted in an active market are classified as "loans and receivables". Loans and receivables are measured at amortized cost using the effective interest method, less any impairment.

The group applies the IFRS 9 simplified approach to measuring expected credit losses which uses a lifetime expected loss allowance for all trade receivables. To measure the expected credit losses, trade receivables have been grouped based on shared credit risk characteristics and the days past due. Trade receivables are written off when there is no reasonable expectation of recovery. Indicators that there is no reasonable expectation of recovery include, amongst others, the failure of a debtor to engage in a repayment plan with the group, and a failure to make contractual payments for a period of greater than 120 days past due. Impairment losses on trade receivables and contract assets are presented as net impairment losses within operating profit. Subsequent recoveries of amounts previously written off are credited against the same line item.

**Previous accounting policy for impairment of trade receivables**

In the prior year, an allowance for doubtful accounts is established when there is objective evidence that the Company will not be able to collect all amounts due according to the original terms of receivables. Significant financial difficulties of the debtor, probability that the debtor will enter into bankruptcy or financial reorganization, and default or delinquency in payments are considered indicators that the trade receivable is impaired. Loans and receivables are included in 'current assets', except for maturities greater than 12 months after the balance sheet date, which are classified as 'non-current assets'.

## (m) Cash and cash equivalents

Cash and cash equivalents include cash on hand and all highly liquid investments with original maturities of three months or less that are convertible to a known amount of cash and bear an insignificant risk of change in value.

## (n) Financial liabilities and equity instruments

Debt and equity instruments are classified as either financial liabilities or as equity in accordance with the substance of the contractual arrangement.

**(i) Equity instruments**

An equity instrument is any contract that evidences a residual interest in the assets of an entity after deducting all of its liabilities. Equity instruments issued by the Company are recognized at the proceeds received, net of direct issue costs.

**(ii) Compound financial instruments**

Compound financial instruments issued by the Group comprise convertible notes denominated in euro that can be converted to share capital at the option of the holder, when the number of shares to be issued is fixed and does not vary with changes in fair value.

The liability component of a compound financial instrument is recognized initially at the fair value of a similar liability that does not have an equity conversion option. The equity component is recognised initially at the difference between the fair value of the compound financial instrument as a whole and the fair value of the liability component. Any directly attributable transaction costs are allocated to the liability and equity components in proportion to their initial carrying amounts.

Subsequent to initial recognition, the liability component of a compound financial instrument is measured at amortized cost using the effective interest method. The equity component of a compound financial instrument is not remeasured.

Interest related to the financial liability is recognized in profit or loss. On conversion, the financial liability is reclassified to equity and no gain or loss is recognized.

**(iii) Other financial liabilities**

Other financial liabilities, including borrowings, are initially measured at fair value, net of transaction costs incurred, and are subsequently measured at amortized cost using the effective interest method, with interest expense recognized on an effective yield basis.

The effective interest method is a method of calculating the amortized cost of a financial liability and of allocating interest expense over the relevant period. The effective interest rate is the rate that exactly discounts estimated future cash payments through the expected life of the financial liability, or, where appropriate, a shorter period.

Borrowings and other financial liabilities are classified as 'non-current liabilities,' other than liabilities with maturities up to one year, which are classified as "current liabilities".

The Company derecognizes financial liabilities when the liability is discharged, cancelled or expired. For all financial liabilities, the fair value approximates its carrying amount.

### (o) Leases

**(i) Determining whether an arrangement contains a lease**

At inception of an arrangement, the Company determines whether such an arrangement is or contains a lease.

At inception or on reassessment of an arrangement that contains a lease, the Company separates payments and other consideration required by such an arrangement into those for the lease and those for other elements on the basis of their relative fair values. If the Company concludes for a finance lease that it is impracticable to separate the payments reliably, then an asset and a liability are recognized at an amount equal to the fair value of the underlying asset. Subsequently, the liability is reduced as payments are made and an imputed finance cost on the liability is recognized using the Company's incremental borrowing rate.

**(ii) Leased assets**

Assets held by the Company under leases that transfer to the Company substantially all of the risks and rewards of ownership are classified as finance leases. The leased assets are measured initially at an amount equal to the lower of their fair value and the present value of the minimum lease payments. Subsequent to initial recognition, the assets are accounted for in accordance with the accounting policy applicable to that asset.

Assets held under other leases are classified as operating leases and are not recognized in the Company's statement of financial position.

**(iii) Lease payments**

Payments made under operating leases are recognized in profit or loss on a straight-line basis over the term of the lease. Lease incentives received are recognized as an integral part of the total lease expense, over the term of the lease.

Minimum lease payments made under finance leases are apportioned between the finance expense and the reduction of the outstanding liability. The finance expense is allocated to each period during the lease term so as to produce a constant periodic rate of interest on the remaining balance of the liability.

## 4. New standards and interpretations not yet adopted

A number of new standards, amendments to standards and interpretations are effective for annual periods beginning after January 1, 2019, and have not been applied in preparing these consolidated financial statements. Those which may be relevant to the Group are set out below. The Group does not plan to adopt these standards early.

**IFRS 16 Leases**

IFRS 16 specifies how a company will recognize, measure, present and disclose leases. The standard provides a single lessee accounting model, requiring lessees to recognize assets and liabilities for all leases unless the lease term is 12 months or less or the underlying asset has a low value. Lessors continue to classify leases as operating or finance, with IFRS 16's approach to lessor accounting substantially unchanged from its predecessor, IAS 17.

The impact on the income statement is that current operating expenses will be replaced by depreciation and interest. Total expenses (depreciation for 'right of use' assets and interest on lease liabilities) are higher in the earlier years of a typical lease and lower in the later years, in comparison with current accounting for operating leases. The main impact on the statement of cash flows is higher cash flows from operating

activities, since cash payments for the principal part of the lease liability are classified in the net cash flow from financing activities by approximately € 1.2 million.

IFRS 16 is effective for annual reporting periods beginning on or after January 1, 2019, with early adoption permitted and is expected to have an effect on our balance sheet of approximately € 2.3 million.

There are no other standards that are not yet effective and that would be expected to have a material impact on the entity in the current or future reporting periods and on foreseeable future transactions.

## 5. Financial Risk Management

### 5.1. Financial risk factors

The Company's activities expose it to a variety of financial risks: market risk (including currency risk, interest rate risk and price risk), credit risk and liquidity risk. The Company's overall financial risk management seeks to minimize potential adverse effects resulting from unpredictability of financial markets on the Company's financial performance.

Financial risk management is carried out by the finance department. The finance department identifies and evaluates financial risks and proposes mitigating actions if deemed appropriate.

**(a) Market risk**

Market risk is the risk that changes in market prices – such as foreign exchange rates, interest rates and equity prices – will affect the Company's income or the value of its holdings of financial instruments. The objective of market risk management is to manage and control market risk exposures within acceptable parameters, while optimizing the return.

***Foreign exchange risk***

Foreign exchange risk arises from future commercial transactions and recognized assets and liabilities in foreign currencies, primarily with respect to the U.S. Dollar. The Company has an exposure associated with the time delay between entering into a contract, budget or forecast and the realization thereof. The Company operates a foreign exchange policy to manage the foreign exchange risk against the functional currency based on the Company's cash balances and the projected future spend per major currency.

At December 31, 2018 there was a net liability in U.S. Dollars of € 0.1 million (2017: € 0.7 million). Foreign currency denominated receivables and trade payables are short term in nature (generally 30 to 45 days). As a result foreign exchange rate movements on receivables and trade payables, during the years presented had an immaterial effect on the financial statements.

At year-end, a substantial amount of our cash balances are denominated in U.S. Dollars. This amount reflects our current expectation of future expenditure in U.S. dollars.

A reasonably possible weakening of the U.S. Dollar by 10% against all other currencies at December 31, 2018 would have affected the measurement of our cash balances denominated in a U.S. Dollar and affected equity and profit or loss by € 2.4 million (2017: € 2.5 million). The analysis assumes that all other variables, in particular interest rates, remain constant.

***Price risk***

The market prices for the production of preclinical and clinical materials and services as well as external contracted research may vary over time. Currently, the commercial prices of any of the Company's product candidates is uncertain. When the development products near the regulatory approval date or potential

regulatory approval date, the uncertainty of the potential sales price decreases. The Company is not exposed to commodity price risk.

Furthermore the Company does not hold investments designated for sale, therefore are not exposed to equity securities price risk.

***Cash flow and fair value Interest rate risk***
The Company's exposure to interest rate risks is limited due to the use of loans with fixed rates. The Company has several loans with fixed interest rates, totaling € 9,386,000 at December 31, 2018 (2017: € 7,244,000). Details on the interest rates and maturities of these loans are provided in Note 13.

**(b) Credit risk**
Credit risk represents the risk of financial loss caused by default of the counterparty. The Company has no large receivables balances with external parties. The Company's principal financial assets are cash and cash equivalents which are held at ABN Amro, Rabobank and Wells Fargo. Our cash management policy is focused on preserving capital, providing liquidity for operations and optimizing yield while accepting limited risk (Short-term credit ratings must be rated A-1/P-1/F1 at a minimum by at least one of the Nationally Recognized Statistical Rating Organizations (NRSROs) specifically Moody's, Standard & Poor's or Fitch. Long-term credit rating must be rated A2 or A at a minimum by at least one NRSRO).

At December 31, 2018 and December 31, 2017, substantially all of our cash and cash equivalents were held at three large institutions, Rabobank, ABN Amro and Wells Fargo. All institutions are highly rated (ratings of Aa3, A1 and A2 for Rabobank, ABN Amro and Wells Fargo respectively) with sufficient capital adequacy and liquidity metrics.

There are no financial assets past due date or impaired. No credit limits were exceeded during the reporting period.

**(c) Liquidity risk**
Liquidity risk represents the risk that an entity will encounter difficulty in meeting obligations associated with its financial liabilities. Prudent liquidity risk management implies ensuring sufficient availability of cash resources for funding of operations and planning to raise cash if and when needed, either through issue of shares or through credit facilities. Management monitors rolling forecasts of the Company's liquidity reserve on the basis of expected cash flow.

The table below analyzes ProQR's undiscounted liabilities into relevant maturity groupings based on the remaining period at year-end until the contractual maturity date:

| | Less than 1 year | Between 1 and 2 years | Between 2 and 5 years | Over 5 years |
|---|---|---|---|---|
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| **At December 31, 2018** | | | | |
| Borrowings | -- | 797 | 8,984 | -- |
| Trade payables and other payables | 8,160 | -- | -- | -- |
| | **8,160** | **797** | **8,984** | **--** |

| | Less than 1 year | Between 1 and 2 years | Between 2 and 5 years | Over 5 years |
|---|---|---|---|---|
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| **At December 31, 2017** | | | | |
| Borrowings | 1,960 | 980 | 5,981 | -- |
| Trade payables and other payables | 6,534 | -- | -- | -- |
| | **8,494** | **980** | **5,981** | **--** |

## 5.2. Capital risk management

The Company's objectives when managing capital are to safeguard the Company's ability to continue as a going concern in order to provide returns for shareholders, benefits for other stakeholders and to maintain an optimal capital structure to reduce the cost of capital.

In order to maintain or adjust the capital structure, the Company may adjust the amount of dividends paid to shareholders (although at this time the Company does not have retained earnings and is therefore currently unable to pay dividends), return capital to shareholders, issue new shares or sell assets to reduce debt.

The total amount of equity as recorded on the balance sheet is managed as capital by the Company.

## 5.3. Fair value measurement

For financial instruments that are measured on the balance sheet at fair value, IFRS 13 requires disclosure of fair value measurements by level of the following fair value measurement hierarchy:

- quoted prices (unadjusted) in active markets for identical assets or liabilities (level 1);
- inputs other than quoted prices included within level 1 that are observable for the asset or liability, either directly (that is, as prices) or indirectly (that is, derived from prices) (level 2); and
- inputs for the asset or liability that are not based on observable market data (that is, unobservable inputs) (level 3).

The carrying amount of all financial assets and financial liabilities is a reasonable approximation of the fair value and therefore information about the fair values of each class has not been disclosed.

# 6. Segment Information

The Company operates in one reportable segment, which comprises the discovery and development of innovative, RNA based therapeutics. The Management Board is identified as the chief operating decision maker. The Management Board reviews the operating results regularly to make decisions about resources and to assess overall performance.

The Company has not generated any sales revenues since inception.

All non-current assets of the Company are located in the Netherlands. The amounts provided to the Management Board with respect to total assets and liabilities are measured in a manner consistent with that of the financial statements.

## 7. Intangible Assets

| | Licenses | Software | Total |
|---|---|---|---|
| | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| **Balance at January 1, 2017** | | | |
| Cost | 39 | 152 | 191 |
| Accumulated amortization | -- | (101) | (101) |
| **Carrying amount** | **39** | **51** | **90** |
| | | | |
| Additions | -- | -- | -- |
| Amortization | -- | (51) | (51) |
| **Movement for the period** | **--** | **(51)** | **(51)** |
| | | | |
| **Balance at December 31, 2017** | | | |
| Cost | 39 | 152 | 191 |
| Accumulated amortization | -- | (152) | (152) |
| **Carrying amount** | **39** | **--** | **39** |
| | | | |
| Additions | -- | -- | -- |
| Impairment charge | (39) | -- | (39) |
| Amortization | -- | -- | -- |
| **Movement for the period** | **(39)** | **--** | **--** |
| | | | |
| **Balance at December 31, 2018** | | | |
| Cost | 39 | 152 | 191 |
| Accumulated amortization | (39) | (152) | (191) |
| **Carrying amount** | **--** | **--** | **--** |

In 2012, the Company acquired an exclusive license from the Massachusetts General Hospital. The initial payment in respect of the license, in the amount of € 39,000 has been impaired and is included in the general and administrative costs for an amount of € 39,000 (2017: € -).

The amortization charge for 2018 is included in the general and administrative costs for an amount of € - (2017: € 51,000).

## 8. Property, Plant and Equipment ('PP&E')

| | Leasehold improvements | Laboratory equipment | Other | Total |
|---|---|---|---|---|
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| **Balance at January 1, 2017** | | | | |
| Cost | 1,847 | 1,957 | 1,283 | 5,087 |
| Accumulated depreciation | (508) | (660) | (481) | (1,649) |
| **Carrying amount** | **1,339** | **1,297** | **802** | **3,438** |
| | | | | |
| Additions | 9 | 47 | 26 | 82 |
| Depreciation | (294) | (409) | (312) | (1,015) |
| Disposals | -- | -- | -- | -- |
| **Movement for the period** | **(285)** | **(362)** | **(286)** | **(933)** |
| | | | | |
| **Balance at December 31, 2017** | | | | |
| Cost | 1,856 | 2,004 | 1,309 | 5,169 |
| Accumulated depreciation | (802) | (1,069) | (793) | (2,664) |
| **Carrying amount** | **1,054** | **935** | **516** | **2,505** |
| | | | | |
| Additions | 18 | 281 | 13 | 312 |
| Depreciation | (296) | (419) | (238) | (953) |
| Disposals | -- | -- | -- | -- |
| **Movement for the period** | **(278)** | **(138)** | **(225)** | **(641)** |
| | | | | |
| **Balance at December 31, 2018** | | | | |
| Cost | 1,874 | 2,285 | 1,322 | 5,481 |
| Accumulated depreciation | (1,098) | (1,488) | (1,031) | (3,617) |
| **Carrying amount** | **776** | **797** | **291** | **1,864** |

The depreciation charge for 2018 is included in the research and development costs for an amount of € 725,000 (2017: € 836,000) and in the general and administrative costs for an amount of € 228,000 (2017: € 179,000).

## 9. Social Security and Other Taxes

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Value added tax | 311 | 396 |
| Wage tax | 932 | -- |
| | **1,243** | **396** |

All receivables are considered short-term and due within one year.

## 10. Prepayments and Other Receivables

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Prepayments | 645 | 1,991 |
| Other receivables | 899 | 73 |
| | **1,544** | **2,064** |

All receivables are considered short-term and due within one year.

## 11. Cash and Cash Equivalents

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Cash at banks | 105,580 | 48,099 |
| Bank deposits | -- | -- |
| | **105,580** | **48,099** |

The cash at banks is at full disposal of the Company.

## 12. Shareholders' Equity

### (a) Share capital

| | Number of ordinary shares | |
|---|---|---|
| | 2018 | 2017 |
| Balance at January 1 | 36,425,014 | 23,346,856 |
| Issued for cash | 6,612,500 | 8,573,975 |
| Issued for services | 112,473 | -- |
| Exercise of share options | 226,098 | 1,034 |
| Treasury shares issued (transferred) | (226,098) | 4,503,149 |
| **Balance at December 31** | **43,149,987** | **36,425,014** |

The authorized share capital of the Company amounting to € 7,200,000 consists of 90,000,000 ordinary shares and 90,000,000 preference shares with a par value of € 0.04 per share. At December 31, 2018, 43,149,987 ordinary shares were issued and fully paid in cash, of which 4,277,051 were held by the Company as treasury shares (2017: 4,503,149).

In 2017, the Company has issued 976,477 shares pursuant to its then-current at-the-market offering program, resulting in proceeds of € 4,138,000, net of € 127,000 of offering expenses.

On June 28, 2017, the Company agreed to the issuance of 1,200,000 ordinary shares to institutional investors at an issue price of $ 5.00 (€ 4.40) per share in a registered direct offering with gross proceeds of € 5,278,000. The closing of the offering was effected on July 3, 2017. Transaction costs amounted to € 414,000, resulting in net proceeds of € 4,864,000.

In November 2017, the Company consummated an underwritten public offering and concurrent registered direct offering of 6,397,498 ordinary shares at an issue price of $ 3.25 (€ 2.76) per share. The gross proceeds from both offerings amounted to € 17,671,000 while the transaction costs amounted to € 988,000, resulting in net proceeds of € 16,683,000.

In September 2018, the Company consummated an underwritten public offering and concurrent registered direct offering of 6,612,500 ordinary shares at an issue price of $ 15.75 per share. The gross proceeds from this offering amounted to € 89,983,000 while the transaction costs amounted to € 5,792,000, resulting in net proceeds of € 84,191,000.

In November 2018, the Company issued 112,473 shares in the aggregate amount of $ 2.5 million, at $ 22.23 (€ 19.46) per share to Ionis Pharmaceuticals, Inc. Under the terms of the agreement, an upfront payment in ordinary shares to its common stock was made to Ionis upon signing the worldwide license agreement. The Company was granted an exclusive worldwide license to QR-1123 and relevant patents. The Company will also make future milestone payments, certain of which will be made in equity and others in cash or equity at the company's discretion, and royalties on net sales of 20% through the royalty term.

On November 7, 2018, the Company filed a shelf registration statement, which permitted: (a) the offering, issuance and sale by the Company of up to a maximum aggregate offering price of $ 300,000,000 of its ordinary shares, warrants and/or units; and (b) as part of the $ 300,000,000, the offering, issuance and sale by

us of up to a maximum aggregate offering price of $ 75,000,000 of its ordinary shares that may be issued and sold under a sales agreement with H.C. Wainwright & Co in one or more at-the-market offerings.

### (b) Equity settled employee benefit reserve

The costs of share options for employees, members of the Supervisory Board and members of the Management Board are recognized in the income statement, together with a corresponding increase in equity during the vesting period, taking into account (deferral of) corporate income taxes. The accumulated expense of share options recognized in the income statement is shown separately in the equity category 'equity settled employee benefit reserve' in the 'statement of changes in equity'. On September 25, 2017, we established a Dutch foundation named Stichting Bewaarneming Aandelen ProQR for holding shares in trust for employees, members of the Management Board and members of the Supervisory Board of the Company and its group companies who from time to time will exercise options under the Company's equity incentive plans.

### (c) Translation reserve

The translation reserve comprises all foreign currency differences arising from the translation of the financial statements of foreign operations.

### (d) Share options

The Company operates an equity-settled share-based compensation plan which was introduced in 2013. Options may be granted to employees, members of the Supervisory Board, members of the Management Board and consultants. The compensation expenses included in operating costs for this plan were € 3,224,000 in 2018 (2017: € 4,024,000), of which € 2,167,000 (2017: € 2,059,000) was recorded in general and administrative costs and € 1,057,000 (2017: € 1,965,000) was recorded in research and development costs based on employee allocation.

Options granted under this stock option plan are exercisable once vested. Any vesting schedule may be attached to the granted options, however the typical vesting period is four years (25% after every year). The options expire ten years after date of grant. Options granted under the stock option plan are granted at exercise prices which equal the fair value of the ordinary shares of the Company at the date of the grant.

The Company accounts for its employee stock options under the fair value method. The fair value of the options is estimated at the date of grant using the Black-Scholes option-pricing model, with on average the following assumptions:

| | Options granted in 2018 | Options granted in 2017 |
|---|---|---|
| Risk-free interest rate | 2.223% | 1.913% |
| Expected dividend yield | 0% | 0% |
| Expected volatility | 80.9% | 88.7% |
| Expected life in years | 5 years | 5 years |

The resulting weighted average grant date fair value of the options amounted to € 2.02 in 2018 (2017: € 3.21). The stock options granted have a 10 year life following the grant date and are assumed to be exercised five years from date of grant for all awards.

Movements in the number of options outstanding and their related weighted average exercise prices are as follows:

| | 2018 | | 2017 | |
|---|---|---|---|---|
| | Number of options | Average exercise price | Number of options | Average exercise price |
| Balance at January 1 | 3,331,875 | € 4.78 | 2,205,989 | € 4.88 |
| Granted | 1,570,366 | € 3.11 | 1,199,447 | € 4.63 |
| Forfeited | (142,467) | € 4.29 | (72,527) | € 5.56 |
| Exercised | (226,098) | € 4.02 | (1,034) | € 3.54 |
| Expired | (22,164) | € 6.42 | -- | -- |
| **Balance at December 31** | **4,511,512** | **€ 4.24** | **3,331,875** | **€ 4.78** |
| Exercisable | 1,683,731 | | 1,148,893 | |

The options outstanding at December 31, 2018 had an exercise price in the range of € 1.11 to € 20.34 (2017: € 1.11 to € 20.34) and a weighted-average contractual life of 7.6 years (2017: 7.9 years).

The weighted-average share price at the date of exercise for share options exercised in 2018 was € 15.36 (2017: € 4.23).

Please refer to Note 23 for the options granted to key management personnel.

## 13. Non-current liabilities

### (a) Borrowings

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Innovation credit | 5,164 | 4,899 |
| Convertible loans | 1,871 | 662 |
| Accrued interest | 2,351 | 1,683 |
| **Total borrowings** | **9,386** | **7,244** |
| Current portion | -- | (1,960) |
| | **9,386** | **5,284** |

**Innovation credit ("Innovatiekrediet")**
On June 1, 2012, ProQR was awarded an Innovation credit by the Dutch government, through its agency RVO of the Ministry of Economic Affairs, for the Company's cystic fibrosis program. Amounts were drawn under this facility in the course of the years 2013 through 2017. The credit covers 35% of the costs incurred in respect of the program up to € 5.0 million.

The credit is interest-bearing at a rate of 10% per annum. Early October 2018 ProQR received a conditional waiver of the € 5 million Innovation credit. The total loan of € 7.4 million including interest will be waived after 3 years if certain conditions are met. The conditions are reviewed by RVO on an annual basis.

On December 10, 2018 ProQR was awarded an Innovation credit by the Dutch government, through its agency RVO of the Ministry of Economic Affairs, for the QR-110 program. Amounts will be drawn under this facility from 2018 through 2021. The credit of € 4.7 million through December 31, 2021 will be used to conduct the Phase 2/3 clinical study and efforts to obtain regulatory and ethical market approval (NDA/MAA) of QR-110 for LCA10, of which € 163,000 has been received in 2018. The credit, including accrued interest of 10% per annum, is repayable depending on obtaining market approval. The credit covers 35% of the costs incurred in respect of the program up to € 4.7 million.

The assets which are co-financed with the granted innovation credits are subject to a right of pledge for the benefit of RVO.

**Convertible loans**

Convertible loans were issued to Amylon Therapeutics B.V. in 2017 and 2018 and are interest-bearing at an average rate of 8% per annum. They are convertible into a variable number of ordinary shares within 36 months at the option of the holder or the Company in case financing criteria are met. Any unconverted loans become payable on demand after 24 -36 months in equal quarterly terms.

In March 2018, we entered into a convertible loan (the “Loan”), pursuant to which we borrowed an aggregate of € 260,000 from the lender. The loan bears interest at a rate of 3% per annum. The outstanding principal and interest under the Loan is convertible into our ordinary shares upon the first to occur of the following events, at the election of the lender for (i) or (ii): (i) our public announcement of a strategic business partnership aimed at joint development of, or development by the partner of, our Huntington’s disease program, in which case the lender may convert the outstanding Loan amount into our ordinary shares at the then-prevailing trading price less a 25% discount; (ii) our public announcement of our decision to independently develop our Huntington’s disease program in the future, in which case the lender may convert the outstanding Loan amount into our ordinary shares at the then-prevailing trading price; or, (iii) on or around March 30, 2020 at the then-prevailing trading price plus a 25% premium. In no event are we required, nor are we permitted, to issue ordinary shares in an amount that exceeds 0.5% of the total number of ordinary shares outstanding immediately prior to the entry into the Loan. The Loan agreement restricts the lender’s ability to transfer the Loan, and prohibits the lender from entering into or engaging in any hedge, swap, short sale, derivative transaction or other agreement or arrangement that transfers any ownership of, or interests in, the Loan or our ordinary shares issued or issuable upon conversion of the Loan. The Loan and the ordinary shares issuable upon conversion of the Loan were issued in reliance on a private placement exemption from registration under the Securities Act of 1933, as amended.

## 14. Current Liabilities

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Borrowings | -- | 1,960 |
| Trade payables | 135 | 546 |
| Social securities and other taxes | -- | 1,019 |
| Pension premiums | 7 | -- |
| Deferred income | 545 | 347 |
| Accrued expenses and other liabilities | 7,473 | 4,622 |
| | **8,160** | **8,494** |

At December 31, 2018, current liabilities included deferred income resulting from funds received for one of our research and innovation programs.

## 15. Other income

| | 2018 | 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Grant income | 5,378 | 870 |
| Rental income from property subleases | 174 | 625 |
| Other income | 209 | -- |
| | **5,761** | **1,495** |

Other income is incidental by nature. In 2015, the European Commission (EC) through its Horizon 2020 program awarded us and our academic partners a grant of € 6 million to support the clinical development of eluforsen (ProQR: € 4.6 million). Horizon 2020 is one of the largest research and innovation programs in the European Union with nearly € 80 billion in available funding for qualified projects from 2014 to 2020. This program has ended at December 31, 2017 and the final amount of € 1.3 million has been recognized as other income in 2018.

On February 9, 2018, the Company entered into a partnership agreement with Foundation Fighting Blindness (FFB), under which FFB has agreed to provide funding of $ 7.5 million for the preclinical and clinical development of QR-421a for Usher syndrome type 2A targeting mutations in exon 13. In 2018 € 2.5 million has been recognized as other income.

On June 5, 2018, the Company entered into a partnership agreement with EB Research Partnership (EBRP) and EB Medical Research Foundation (EBMRF) under which EBRP and EBMRF have agreed to provide funding of $ 5.0 million for the clinical development of QR-313 for Dystrophic Epidermolysis Bullosa targeting mutations in exon 73. In 2018 € 1.3 million has been recognized as other income.

Grants are recognized in other income in the same period in which the related R&D costs are recognized.

## 16. Research and Development Costs

Research and development costs amounted to € 29,514,000 in 2018 (2017: € 31,153,000) and comprise allocated employee costs, the costs of materials and laboratory consumables, the costs of external studies

including, amongst others, clinical studies and toxicology studies and external research, license- and IP-costs and allocated other costs.

## 17. Employee Benefits

| | 2018 | 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Wages and salaries | 11,558 | 11,855 |
| Social security costs | 1,346 | 1,285 |
| Pension costs – defined contribution plans | 868 | 860 |
| Equity-settled share based payments | 3,224 | 4,024 |
| | **16,996** | **18,024** |
| Average number of employees for the period | 127.7 | 139.9 |

Employees per activity at December 31 (converted to FTE):

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| Research and Development | 89.2 | 96.2 |
| General and Administrative | 29.6 | 34.0 |
| | **118.8** | **130.2** |

Of all employees 112.8 FTE are employed in the Netherlands (2017: 125.2 FTE).

Included in the wages and salaries for 2018 is a credit of € 1,294,000 (2017: € 723,000) with respect to WBSO subsidies.

## 18. Financial Income and Expense

| | 2018 | 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| **Interest income** | | |
| Current accounts and deposits | 189 | 90 |
| **Interest costs** | | |
| Interest on loans and borrowings | (810) | (596) |
| **Foreign exchange result** | | |
| Net foreign exchange benefit/(loss) | (171) | (2,669) |
| | **(792)** | **3,175** |

## 19. Income Taxes

The calculation of the tax charge is as follows:

| | 2018 | 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Income tax provision based on domestic rate | 9,106 | 10,918 |
| Tax effect of: | | |
| Non-deductible expenses | (818)- | (634) |
| Deductible expenses | 1,448 | -- |
| Tax incentives | -- | -- |
| Current year losses for which no deferred tax asset was recognized | (9,710) | (10,257) |
| Change in unrecognized deductible temporary differences | (25) | (25) |
| **Income tax charge** | **1** | **2** |
| Effective tax rate | 0% | 0% |

Due to the operating losses incurred since inception the Company has no tax provisions as of the balance sheet date. Furthermore, no significant temporary differences exist between accounting and tax results.

Realization of deferred tax assets is dependent on future earnings, if any, the timing and amount of which are uncertain. Accordingly, the Company has not yet recognized any deferred tax asset related to operating losses. As per December 31, 2018, the Company has a total amount of € 162.6 million (2017: € 123.9 million) tax loss carry-forwards available for offset against future taxable profits. According to current tax regulations the first amount of the tax loss carry-forwards will expire in 2021.

## 20. Earnings Per Share

### (a) Basic and diluted earnings per share

Basic earnings per share are calculated by dividing the result attributable to equity holders of the Company by the weighted average number of shares outstanding during the year.

| | 2018 | 2017 |
|---|---|---|
| Result attributable to equity holders of the Company (€ 1,000) | (36,894) | (43,637) |
| Weighted average number of shares outstanding | 34,052,520 | 25,374,807 |
| **Basic (and diluted) earnings per share (€ per share)** | **(1.08)** | **(1.72)** |

### (b) Diluted earnings per share

For the periods included in these financial statements, the share options are not included in the diluted earnings per share calculation as the Company was loss-making in all periods. Due to the anti-dilutive nature of the outstanding options, basic and diluted earnings per share are equal.

### (c) Dividends per share

The Company did not declare dividends for any of the years presented in these financial statements.

## 21. Operational Leases

Since 2012, the Company is domiciled in Leiden, the Netherlands, where it currently has entered into rental agreements for laboratory space and offices and since late 2018 in Cambridge, Massachusetts, USA.

We lease facilities of approximately 2,960 square meters in total, located at Zernikedreef in Leiden, the Netherlands, where our headquarters and our laboratories are located. The lease for this facility terminates on December 31, 2020, and subject to the provisions of the lease, may then be renewed for subsequent 5 year terms. In May 2018, we entered into an agreement to lease additional office space in the US, at CIC Cambridge. Per January 2019, we rent an office of approximately 60 square meters, located at 245 Main Street, Cambridge, MA 02142. We believe that our existing facilities are adequate to meet current needs and that suitable alternative spaces will be available in the future on commercially reasonable terms.

The lease expenditure charged to the income statement in 2018 amounts to € 1,813,000 (2017: € 2,103,000). The future aggregate minimum lease payments under non-cancellable operating leases are as follows:

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Less than 1 year | 1,233 | 1,607 |
| Between 1 and 5 years | 1,233 | 3,312 |
| More than 5 years | -- | -- |
| | **2,466** | **4,919** |

The Company leased out a part of its office in the U.S. and the Netherlands during 2017 and early 2018. In 2018, total sublease income amounted to € 174,000 (2017: € 625,000), which is recorded in other income. At 31 December, the future minimum lease payments under non-cancellable leases are receivable as follows:

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Less than 1 year | -- | 174 |
| Between 1 and 5 years | -- | -- |
| More than 5 years | -- | -- |
| | **--** | **174** |

## 22. Commitments and Contingencies

### (a) Claims

There are no claims known to management related to the activities of the Company.

### (b) Patent license agreements

On October 26, 2018, we and Ionis Pharmaceuticals, Inc. entered into a License Agreement, pursuant to which Ionis granted an exclusive, worldwide, royalty-bearing license to us to develop and commercialize certain pharmaceutical products, including the product designated by Ionis as IONIS-RHO-2.5Rx, which has been re-designated by us as QR-1123, for the prevention or treatment of retinitis pigmentosa in humans, including patient screening. Ionis also granted to the Company certain sub-license rights. Under the License

Agreement, we are required to make an upfront payment of an aggregate of up to $ 6.0 million in installments, and certain payments up to an aggregate of $ 20.0 million upon the satisfaction of certain development and sales milestones. In addition, Ionis is entitled to royalty payments in the double digits of aggregate annual net sales, subject to minimum sales in certain circumstances, and subject to reduced rates in certain circumstances. The royalty term lasts on a product-by-product and country-by-country basis, until the later of the expiration of the patent rights licensed to us and the expiration of regulatory-based exclusivity for such product in such country. The License Agreement may also be terminated by either party based upon certain uncured material breach by, or insolvency of, the other party, or by us at any time with advanced notice. In connection with the upfront payments and development milestone payments, we also simultaneously entered into a Stock Purchase Agreement with Ionis, pursuant to which we agreed to issue an aggregate of $ 2.5 million of ordinary shares to satisfy the first installment upfront payment, and the remaining installment of the upfront payment in ordinary shares determined upon the due date of such installment. In addition, the Stock Purchase Agreement provides for the ability for us, at our discretion, to pay the development milestone payments in ordinary shares when such payments are due. We may not issue ordinary shares to Ionis to the extent that such issuance would result in Ionis owning in excess of 18.5% of our issued and outstanding shares, nor may we issue ordinary shares if such issuance, together with previous issuances under the Stock Purchase Agreement, would exceed 19.9% of our outstanding ordinary shares as of the date of the execution of the Stock Purchase Agreement. Under these circumstances, we are required to pay the remainder of the upfront and/or development milestone payments in cash. In addition, in connection with the Stock Purchase Agreement, we also entered into an Investor Agreement with Ionis, pursuant to which we agreed to register for resale the ordinary shares issued by us under the Stock Purchase Agreement, under the circumstances described in the Investor Agreement. The Investor Agreement also contains customary covenants related to our registration of such shares, preparation of filings in connection therewith and indemnification of Ionis. The Investor Agreement also contains lockup provisions prohibiting the disposition of our ordinary shares issued under the Stock Purchase Agreement for a period of 12 months from the applicable issuance date, as well as voting provisions requiring Ionis to vote its ordinary shares in accordance with the recommendations of our board of directors, in each case subject to certain exceptions

In April 2014 the Company entered into a Patent License Agreement with Radboud University Medical Center, or Radboud in the field of antisense oligonucleotide-based therapy for Leber's Congenital Amaurosis, or LCA. Under the terms of this license agreement, the Company has an exclusive, sublicensable, world-wide royalty-bearing license under certain Radboud patent rights to develop, make, have made, use, sell offer for sale and import of certain licensed products of Radboud for use in all prophylactic and therapeutic uses in the field of LCA. Pursuant to the terms of the license agreement, the Company is obligated to pay Radboud net-sales-related royalties which shall be determined on a product-by-product and country-by-country basis. If the Company required to pay any third party royalties, it may deduct that amount from that which is owed to Radboud. Radboud shall provide human resources, materials, facilities and equipment that are necessary for preclinical and clinical trials and if the Company does not purchase such trial facilities from Radboud, it is required to pay an increased net-sales-related royalty. In the Company's sole discretion, it may elect to convert the obligation to pay net-sales-related royalties into one of the two lump-sum royalty options depending on whether the Company elects to convert prior to or after regulatory approval has been filed. The license agreement will remain in effect until the date on which all patent applications and all granted patents ensuing from such applications have expired or is terminated earlier in accordance with the agreement. Either party may terminate the agreement if the other party is in default of a material obligation under the agreement which has not been cured within 30 days of notice of such default. Either party may also terminate the agreement if the other party declares bankruptcy, dissolves, liquidates or the like. Radboud may also terminate the agreement if the Company does not pay any amount owed under the agreement and such payment remains overdue for at least 30 days after receiving notice from Radboud of the amount due.

In June 2015, we entered into another license agreement with Radboud. Under the terms of this license agreement, the Company has an exclusive, sublicensable, world-wide royalty-bearing license under certain Radboud patent rights to develop, make, have made, use, sell offer for sale and import of certain licensed products of Radboud for use in all prophylactic and therapeutic uses in the field of Usher syndrome. Pursuant to the terms of the license agreement, the Company is obligated to pay Radboud net-sales-related royalties which shall be determined on a product-by-product and country-by-country basis. If the Company is required to pay any third party royalties, it may deduct that amount from that which is owed to Radboud. Radboud shall provide human resources, materials, facilities and equipment that are necessary for preclinical and clinical trials and if the Company does not purchase such trial facilities from Radboud, it is required to pay an increased net-sales-related royalty. In the Company's sole discretion, it may elect to convert the obligation to pay net-sales-related royalties into one of the two lump-sum royalty options depending on whether it elects to convert prior to or after regulatory approval has been filed. The license agreement will remain in effect until the date on which all patent applications and all granted patents ensuing from such applications have expired or is terminated earlier in accordance with the agreement. Either party may terminate the agreement if the other party is in default of a material obligation under the agreement which has not been cured within 30 days of notice of such default. Either party may also terminate the agreement if the other party declares bankruptcy, dissolves, liquidates or the like. Radboud may also terminate the agreement if the Company does not pay any amount owed under the agreement and such payment remains overdue for at least 30 days after receiving notice from Radboud of the amount due.

In January 2018, the Company entered into a license agreement with Inserm Transfert SA and Assistance-Publique-Hôpiteaux de Paris. Under the terms of the agreement, the Company has a world-wide, exclusive, royalty-bearing license under patent rights belonging to Inserm Transfert SA and other co-owners to develop, have developed, make, have made, use, have used and sell, have sold or otherwise distribute certain licensed products related to antisense oligonucleotides for treating LCA and method of treatment claims relating to modulation of the splicing of the CEP290 gene product. The Company has the right to grant sublicenses to third parties subject to certain limitations such as the sublicensee's activities do not conflict with the public order or ethical obligations of Inserm Transfert SA or any co-owner and do not tarnish the image of Inserm Transfert SA or any co-owner. In partial consideration of the rights and licenses granted by the license agreement, the Company is required to make payments upon the completion of certain milestones: completion of a clinical trial more advanced than First in Man, such as a phase IIb; and the first marketing authorization or any foreign equivalent for a first product. In further consideration of the rights and license granted under the agreement, the Company shall pay to Inserm Transfert SA a running royalty on net sales of products sold by us or our sublicensee. Unless terminated earlier pursuant to termination provisions of Agreement, the license agreement will remain in effect on a country-by-country basis, until the later to occur of the following events (i) the invalidation or expiration of the last to expire or to be invalidated patent rights which covers the manufacture, use or sale of the product in said country or until the expiration of the exclusive commercialization right granted by a regulatory agency to a product as an orphan drug or (ii) five years after the first commercial sale of a product in the country in which the product is sold. The agreement may be terminated by either party in the event of an uncured breach by the non-breaching party. Inserm Transfert SA may terminate the agreement if we become the subject of voluntary or involuntary winding-up proceedings or judicial recovery, if the Company or its sublicensees interrupt development activities for at least one year, if the Company or its sublicensees interrupt commercialization for more than twelve months after the first commercialization in a country, if the Company does not commercialize a product within two years following our obtaining of marketing approval in a country, or if the Company or our sublicensees do not put a product into commercial use and do not keep products reasonably available to the public within twelve years of the effective date of the agreement.

In January 2016, the Company entered into an agreement with Leiden University Medical Center, or LUMC, which gives us a world-wide, exclusive, royalty-bearing license in the field of amyloid beta related diseases,

notably Alzheimer's disease and HCHWA-D, under certain patent rights of LUMC regarding antisense oligonucleotide based therapies. This license agreement contains certain diligence obligations for the Company coupled to milestone payments and complements the Company's intellectual property relating to its CNS program. On September 12, 2017, this program was transferred to Amylon Therapeutics B.V., in which the Company maintains a majority ownership.

In January 2017, the Company entered into an agreement with LUMC, which gives us a world-wide, exclusive, royalty-bearing license in the field of Huntington's disease, under certain patent rights of LUMC regarding antisense oligonucleotide based therapies. This license agreement contains certain diligence obligations for the Company coupled to milestone payments and complements the Company's intellectual property relating to the HD program.

In 2012, the Company and the General Hospital Corporation (MGH) have entered into a Patent License Agreement for the Company's CF program pursuant to which the Company may have certain royalty and milestone obligations. The Company is also obligated to pay MGH up to $ 700,000 (€ 611,000) in milestone payments upon the achievement of certain development and regulatory milestones and, beginning after its first commercial sale of a product covered by the licensed patent rights, a $ 10,000 (€ 9,000) annual license fee which is creditable against royalties due to MGH in the same calendar year. In addition, the Company is obligated to pay MGH 2% of any net sales by the Company, its affiliates or sublicensees on licensed products made or sold in the United States, as well as a low double-digit percentage of any payments the Company may receive from any sublicensee anywhere in the world.

### (c) Clinical support agreements

In August 2014, the Company entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide the Company with up to $ 3 million (€ 2.6 million) to support the clinical development of eluforsen.

Pursuant to the terms of the agreement, the Company is obligated to make a one-time milestone payment to CFFT of up to approximately $ 16 million (€ 14 million), payable in three equal annual installments following the first commercial sale of eluforsen, the first of which is due within 90 days following the first commercial sale. The Company is also obligated to make a one-time milestone payment to CFFT of up to $ 3 million (€ 2.6 million) if net sales of eluforsen exceed $ 500 million (€ 437 million) in a calendar year. Lastly, the Company is obligated to make a payment to CFFT of up to approximately $ 6 million (€ 5 million) if it transfers, sells or licenses eluforsen other than for certain clinical or development purposes, or if the Company enters into a change of control transaction prior to commercialization. However, the payment in the previous sentence may be set-off against the $ 16 million milestone payment. Either CFFT or the Company may terminate the agreement for cause, which includes the Company's material failure to achieve certain commercialization and development milestones. The Company's payment obligations survive the termination of the agreement.

On February 9, 2018, the Company entered into an agreement with Foundation Fighting Blindness (FFB), under which FFB will provide funding of $ 7.5 million (€ 6.6 million) to advance QR-421a into the clinic and will receive future milestone payments.

Pursuant to the terms of the agreement, the Company is obligated to make a one-time milestone payment to FFB of up to approximately $ 37.5 million (€ 32.8 million), payable in four equal annual installments following the first commercial sale of QR-421a, the first of which is due within 60 days following the first commercial sale. The Company is also obligated to make a payment to FFB of up to approximately $ 15 million (€ 13.1 million) if it transfers, sells or licenses QR-421a other than for certain clinical or development purposes, or if the Company enters into a change of control transaction. However, the payment in the previous sentence may be set-off against the $ 37.5 million milestone payment. Either FFB or the Company may terminate the

agreement for cause, which includes the Company's material failure to achieve certain commercialization and development milestones. The Company's payment obligations survive the termination of the agreement.

On June 5, 2018, the Company entered into a partnership agreement with EB Research Partnership (EBRP) and EB Medical Research Foundation (EBMRF) under which EBRP and EBMRF have agreed to provide funding of $ 5.0 million for the clinical development of QR-313 for Dystrophic Epidermolysis Bullosa targeting mutations in exon 73.

Pursuant to the terms of the agreement, the Company shall, during the period starting upon completing a Successful Clinical Study, pay EBRP the total Actual Award in 12 equal semi-annual installments of the Actual Award made by EBRP. ProQR shall have the option, at its discretion, to pay the amount for each installment in ProQR Therapeutics N.V. shares at the price of market close on the payment due date. In addition to the payment in subparagraph (a) above, ProQR shall pay a return on investment to EBRP in an amount equal of 1.36 times the Actual Award at the first anniversary of First Commercial Sale; 1.36 times the Actual Award at the second anniversary of First Commercial Sale; 1.36 times the Actual Award at the third anniversary of First Commercial Sale; and 1.0 times the Actual Award when aggregate Net Sales of the Product exceed $ 100 million.

In the event of a License Transaction by ProQR or a Change of Control Transaction (collectively a "Disposition Transaction"): (i) ProQR shall pay to EBRP 33.3 percent of any consideration received by ProQR in connection with such transaction (whether up front or in subsequent milestone or other payments and whether in cash or other property) not to exceed four (4) times the amount of the Actual Award (the "Disposition Payment"), provided that (i) the amount of the actual total payment previously made by ProQR under Section 2(a) shall be deducted from the amount of the "Disposition Payment".

### (d) Research and development commitments

The Company has research and development commitments, mainly with CRO's, amounting to € 8,114,000 at December 31, 2018 (2017: € 7,704,000). Of these obligations an amount of € 5,807,000 is due in 2019, the remainder is due in 1 to 5 years.

## 23. Related-Party Transactions

Details of transactions between the Company and related parties are disclosed below.

### (a) Compensation of the Supervisory Board

The remuneration of the Supervisory Board members in 2018 is set out in the table below:

| | 2018 | | | |
|---|---|---|---|---|
| | Short term employee benefits | Post employment benefits | Share-based payment | Total |
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| Mr. Dinko Valerio | 36 | -- | 69 | 105 |
| Mr. Antoine Papiernik | 72 | -- | -- | 72 |
| Ms. Alison Lawton | 31 | -- | 75 | 106 |
| Mr. Paul Baart | 80 | -- | -- | 80 |
| Mr. James Shannon | 33 | -- | 73 | 106 |
| | **252** | **--** | **217** | **469** |

The remuneration of the Supervisory Board members in 2017 is set out in the table below:

| | 2017 | | | |
|---|---|---|---|---|
| | Short term employee benefits | Post employment benefits | Share-based payment | Total |
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| Mr. Dinko Valerio | 36 | -- | 87 | 123 |
| Mr. Henri Termeer | 28 | -- | 160 | 188 |
| Mr. Antoine Papiernik | 76 | -- | -- | 76 |
| Ms. Alison Lawton | 31 | -- | 99 | 130 |
| Mr. Paul Baart | 84 | -- | -- | 84 |
| Mr. James Shannon | 33 | -- | 92 | 125 |
| | **288** | **--** | **438** | **726** |

As at December 31, 2018:

- Mr. Dinko Valerio holds 1,043,420 ordinary shares in the Company, as well as 115,925 options. These options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant. In 2017, Mr. Valerio was granted 32,164 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an average exercise price of € 4.65 per option. In 2018, Mr. Valerio was granted 27,500 options at an average exercise price of € 2.74 per option.
  On September 12, 2017, Mr. Valerio provided a convertible loan to Amylon Therapeutics B.V. This loan is interest-bearing at an average rate of 8% per annum and is convertible into a variable number of ordinary shares within 36 months at the option of the holder or the Company in case financing criteria are met. Any unconverted loans become payable on demand after 24 months in equal quarterly terms.
- Mr. Antoine Papiernik does not hold any shares or options in the Company. As a managing partner of Sofinnova Partners SAS, the management company of Sofinnova Capital VII FCPR, holder of 2,764,194 ordinary shares, Mr. Papiernik may be deemed to have share voting and investment power with respect to such shares.
- Ms. Alison Lawton holds 96,473 options. In 2017, Ms. Lawton was granted 32,164 options under the Option Plan to acquire depositary receipts issued for ordinary shares with an average exercise price of € 4.65 per option. In 2018, Ms. Lawton was granted 27,500 options with an average exercise price of € 2.74 per option. Under these option grants options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant.
- Mr. Paul Baart does not hold any shares or options in the Company.
- Mr. James Shannon holds 61,538 ordinary shares in the Company and 92,733 options. In 2017, Mr. Shannon was granted 32,164 options under the Option Plan to acquire depositary receipts issued for ordinary shares at an exercise price of € 4.65 per option. In 2018, Mr. Shannon was granted 27,500 options at an exercise price of € 2.74 per option. Under these option grants options vest in four annual equal tranches of 25% starting for the first time as of the first anniversary of the date of grant.

## (b) Compensation of key management

Our Management Board is supported by our officers, or senior management. The total remuneration of the Management Board and senior management in 2018 amounted to € 5,481,000.

The details are set out in the table below:

| | 2018 | | | |
|---|---|---|---|---|
| | Short term employee benefits | Post employment benefits | Share-based payment | Total |
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| Mr. D.A. de Boer[1] | 726 | 9 | 668 | 1,403 |
| Mr. R.K. Beukema[2] | 809 | 16 | 464 | 1,289 |
| **Management Board** | **1,535** | **25** | **1,132** | **2,692** |
| Senior Management | 1,726 | 64 | 999 | 2,789 |
| | **3,261** | **89** | **2,131** | **5,481** |

1 Short term employee benefits includes a bonus for Mr. Daniel de Boer of € 281,000 based on goals realised in 2018.
2 Short term employee benefits includes a bonus for Mr. René Beukema of € 134,000 based on goals realised in 2018 and a severance payment of € 324,000

The total remuneration of the Management Board and senior management in 2017 amounted to € 5,096,000 with the details set out in the table below:

| | 2017 | | | |
|---|---|---|---|---|
| | Short term employee benefits | Post employment benefits | Share-based payment | Total |
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| Mr. D.A. de Boer[1] | 570 | 8 | 622 | 1,200 |
| Mr. R.K. Beukema[2] | 411 | 15 | 261 | 687 |
| **Management Board** | **981** | **23** | **883** | **1,887** |
| Senior Management | 1,719 | 66 | 1,424 | 3,209 |
| | **2,700** | **89** | **2,307** | **5,096** |

1 Short term employee benefits includes a bonus for Mr. Daniel de Boer of € 217,000 based on goals realised in 2017.
2 Short term employee benefits includes a bonus for Mr. René Beukema of € 113,000 based on goals realised in 2017.

As at December 31, 2018:

- Mr. Daniel de Boer holds 705,309 ordinary shares in the Company as well as 828,623 options. In 2017, Mr. de Boer was awarded 239,717 options to acquire ordinary shares at an exercise price of € 4.65 per option. In 2018, he was awarded 379,285 options at an exercise price of € 2.74 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 8.1 years at December 31, 2018.
- Mr. René Beukema holds 346,239 ordinary shares in the Company as well as 440,013 options. In 2017, Mr. Beukema was awarded 101,408 options to acquire ordinary shares at an exercise price of € 4.65 per

option. In 2018, he was awarded 140,932 options at an exercise price of € 2.74 per option. These options vest over four years in equal annual installments and had a remaining weighted-average contractual life of 7.2 years at December 31, 2018. Mr. Beukema left the Company January 1, 2019.

ProQR does not grant any loans, advanced payments and guarantees to members of the Management and Supervisory Board.

## 24. Subsequent events

On March 26, 2019, the Company announced the strategic spin out of the Dystrophic Epidermolysis Bullosa (DEB) activities into the newly formed company, Wings Therapeutics. This company is formed and financed by EB Research Partnership (EBRP), the largest global non-profit dedicating to treating and curing EB. Wings Therapeutics will focus on developing therapies for DEB and continue to conduct clinical trials with QR-313 in exon 73 as well as progress other RNA molecules that are designed for other mutations that cause DEB. ProQR has a minority stake in Wings Therapeutics and will be eligible for milestone and royalty rights to commercial products. The financial impact on the Company is estimated to be immaterial.

# Company balance sheet at December 31, 2018

(Before appropriation of result)

| | Note | December 31, 2018 | December 31, 2017 |
|---|---|---|---|
| | | *€ 1,000* | *€ 1,000* |
| **ASSETS** | | | |
| **Non-current assets** | | | |
| Financial fixed assets | 27 | 70 | 0 |
| | | **70** | **0** |
| **Current assets** | | | |
| Social securities and other taxes | 28 | 291 | 379 |
| Prepayments and other receivables | 29 | 31,885 | 20,615 |
| Cash and cash equivalents | 30 | 100,560 | 47,029 |
| | | **132,736** | **68,023** |
| **TOTAL ASSETS** | | **132,806** | **68,023** |
| **EQUITY** | | | |
| **Shareholders' equity** | | | |
| Share capital | | 1,726 | 1,457 |
| Share premium reserve | | 235,744 | 148,763 |
| Equity settled employee benefits reserve | | 10,780 | 8,377 |
| Translation reserve | | 108 | 136 |
| Accumulated deficit | | (118,396) | (75,733) |
| Unappropriated result | | (36,126) | (43,484) |
| | **31** | **93,836** | **39,516** |
| **LIABILITIES** | | | |
| **Provisions** | **32** | **30,214** | **20,710** |
| **Non-current liabilities** | | | |
| Borrowings | 33 | 7,351 | 6,582 |
| | | **7,351** | **6,582** |
| **Current liabilities** | | | |
| Trade payables | | 79 | 184 |
| Social securities and other taxes | | -- | 214 |
| Pension premiums | | 6 | -- |
| Deferred income | | -- | 347 |
| Other current liabilities | | 1,320 | 470 |
| | | **1,405** | **1,215** |
| **TOTAL LIABILITIES** | | **38,970** | **28,507** |
| **TOTAL EQUITY AND LIABILITIES** | | **132,806** | **68,023** |

The accompanying notes are an integral part of these financial statements.

## Company income statement for the year ended December 31, 2018

| | Note | 2018 | 2017 |
|---|---|---|---|
| | | *€ 1,000* | *€ 1,000* |
| Share in results of participating interests, after taxation | 27 | (31,932) | (34,123) |
| Other result after taxation | | (4,194) | (9,361) |
| **Net result for the year** | | **(36,126)** | **(43,484)** |

The accompanying notes are an integral part of these financial statements.

# Notes to the Company financial statements for the year ended December 31, 2018

## 25. General

The company financial statements are part of the 2018 financial statements of ProQR Therapeutics N.V. (the 'Company') and have been prepared in accordance with the legal requirements of Part 9, Book 2 of the Netherlands Civil Code.

With reference to the income statement of the company, use has been made of the exemption pursuant to Section 402 of Book 2 of the Netherlands Civil Code.

## 26. Principles for the measurement of assets and liabilities and the determination of the result

For setting the principles for the recognition and measurement of assets and liabilities and determination of the result for its company financial statements, the Company makes use of the option provided in section 2:362(8) of the Netherlands Civil Code. This means that the principles for the recognition and measurement of assets and liabilities and determination of the result (hereinafter referred to as principles for recognition and measurement) of the company financial statements of the Company are the same as those applied for the consolidated IFRS financial statements. See page 55 for a description of these principles.

### Participating interests in group companies

Participating interests in group companies are valued using the equity method, applying the IFRS accounting policies endorsed by the European Union. Following the adoption of IFRS 9 by the group, and our interpretation of the Dutch Accounting Standard 100.107A, the company shall, upon identification of a credit loss on an intercompany loan and/or receivable, eliminate the carrying amount of the intercompany loan and/or receivable for the value of the identified credit loss.

### Result of participating interests

The share in the result of participating interests consists of the share of the Company in the result of these participating interests. In so far as gains or losses on transactions involving the transfer of assets and liabilities between the Company and its participating interests or between participating interests themselves can be considered unrealised, they have not been recognised.

## 27. Financial fixed assets

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Participating interests in group companies | 70 | 0 |
| | **70** | **0** |

Movements in financial fixed assets were as follows:

| | Participating interests in group companies | Total |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Net asset value as of January 1 | 0 | 0 |
| Share in results of participating interests, after taxation | (31,932) | (31,932) |
| Exchange differences | (28) | (28) |
| Change in provisions for negative net asset value | 32,030 | 32,030 |
| **Net asset value as of December 31** | **70** | **70** |

At December 31, 2018, the Company, having its statutory seat in Leiden, the Netherlands, is the ultimate parent company of the following consolidated participating interests:

| Name | Location | Share in issued capital |
|---|---|---|
| ProQR Therapeutics Holding B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics I B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics II B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics III B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics IV B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics VI B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics VII B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics VIII B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics IX B.V. | Leiden, the Netherlands | 100% |
| ProQR Therapeutics I Inc. | Delaware, United States | 100% |
| Amylon Therapeutics B.V. | Leiden, the Netherlands | 80% |
| Amylon Therapeutics Inc. | Delaware, Unites States | 80% (100% held by Amylon Therapeutics B.V. |

ProQR Therapeutics Holding B.V. is an intermediate holding company and the only subsidiary owned directly by ProQR Therapeutics N.V..

ProQR Therapeutics N.V. is also statutory director of Stichting Bewaarneming Aandelen ProQR ("ESOP Foundation"). For details on the accounts receivable from participating interests and the other receivables, reference is made to note 29.

## 28. Social Security and Other Taxes

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Value added tax | 291 | 379 |
| | **291** | **379** |

All receivables are considered short-term and due within one year.

## 29. Prepayments and Other Receivables

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Accounts receivable from group companies | 31,719 | 20,400 |
| Prepayments | 166 | 210 |
| Other receivables | -- | 5 |
| | **31,885** | **20,615** |

All receivables are considered short-term and due within one year.

## 30. Cash and Cash Equivalents

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Cash at banks | 100,560 | 47,029 |
| Bank deposits | -- | -- |
| | **100,560** | **47,029** |

The cash at banks is at full disposal of the Company.

## 31. Shareholders' equity

| | Share Capital | Share Premium | Equity Settled Employee Benefit Reserve | Trans-lation Reserve | Accumu-lated Deficit | Unappro-priated result | Total Equity |
|---|---|---|---|---|---|---|---|
| | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* | *€ 1,000* |
| **Balance at January 1, 2017** | **934** | **123,597** | **4,353** | **(15)** | **(36,630)** | **(39,103)** | **53,136** |
| Retained result | -- | -- | -- | -- | (39,103) | 39,103 | -- |
| Foreign exchange differences | -- | -- | -- | 151 | -- | -- | 151 |
| Recognition of share-based payments | -- | -- | 4,024 | -- | -- | -- | 4,024 |
| Issue of ordinary shares | 343 | 25,342 | -- | -- | -- | -- | 25,685 |
| Issue of treasury shares | 180 | (180) | -- | -- | -- | -- | -- |
| Share options exercised | 0 | 4 | -- | -- | -- | -- | 4 |
| Result for the year | -- | -- | -- | -- | -- | (43,484) | (43,484) |
| **Balance at December 31, 2017** | **1,457** | **148,763** | **8,377** | **136** | **(75,733)** | **(43,484)** | **39,516** |
| Retained result | -- | -- | -- | -- | (43,484) | 43,484 | -- |
| Foreign exchange differences | -- | -- | -- | (28) | -- | -- | (28) |
| Recognition of share-based payments | 4 | 2,185 | 3,224 | -- | -- | -- | 5,413 |
| Issue of ordinary shares | 265 | 83,926 | | -- | -- | -- | 84,191 |
| Share options lapsed | -- | -- | (97) | -- | 97 | -- | -- |
| Share options exercised | -- | 870 | (724) | -- | 724 | | 870 |
| Result for the year | -- | -- | -- | -- | -- | (36,126) | (36,126) |
| **Balance at December 31, 2018** | **1,726** | **235,744** | **10,780** | **108** | **(118,396)** | **(36,126)** | **93,836** |

The 2017 result was added to the accumulated deficit in accordance with the resolution of the Annual General Meeting of shareholders. At the upcoming Annual General Meeting of shareholders, it will be proposed to add the 2018 result to the accumulated deficit. For more details we refer to note 12 to the consolidated financial statements.

## Reconciliation of shareholders' equity and net result per the consolidated financial statements with shareholders' equity and net result per the company financial statements

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| **Shareholders' equity according to the consolidated balance sheet** | **92,685** | **39,325** |
| Share in results of participating interests with negative equity | 1,151 | 191 |
| **Shareholders' equity according to the company balance sheet** | **93,836** | **39,516** |

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| **Net result according to the consolidated profit and loss account** | **(37,086)** | **(43,675)** |
| Share in results of participating interests with negative equity | 960 | 191 |
| **Net result according to the company profit and loss account** | **(36,126)** | **(43,484)** |

## 32. Provisions

| Provision for negative equity group companies | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| **Balance at January 1** | **20,710** | **12,175** |
| Provisions made during the year | 9,504 | 8,535 |
| **Balance at December 31** | **30,214** | **20,710** |

## 33. Borrowings

| | December 31, 2018 | December 31, 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Innovation credit | 5,000 | 4,899 |
| Accrued interest | 2,351 | 1,683 |
| **Total borrowings** | **7,351** | **6,582** |

**Innovation credit ("Innovatiekrediet")**

On June 1, 2012, ProQR was awarded an Innovation credit by the Dutch government, through its agency RVO of the Ministry of Economic Affairs, for the Company's cystic fibrosis program. Amounts were drawn under this facility in the course of the years 2013 through 2017. The credit covers 35% of the costs incurred in respect of the program up to € 5.0 million.

The credit is interest-bearing at a rate of 10% per annum. Early October 2018 ProQR received a conditional waiver of the € 5 million Innovation credit. The total loan of € 7.4 million including interest will be waived after 3 years if certain conditions are met. The conditions are reviewed by RVO on an annual basis.

The assets which are co-financed with the granted innovation credits are subject to a right of pledge for the benefit of RVO.

## 34. Commitments and Contingencies

### (a) Claims

There are no claims known to management related to the activities of the Company.

### (b) Clinical support agreement

In August 2014, the Company entered into an agreement with Cystic Fibrosis Foundation Therapeutics, Inc., or CFFT, a subsidiary of the Cystic Fibrosis Foundation, pursuant to which CFFT agreed to provide the Company with up to $ 3 million (€ 2.6 million) to support the clinical development of eluforsen.

Pursuant to the terms of the agreement, the Company is obligated to make a one-time milestone payment to CFFT of up to approximately $ 16 million (€ 14 million), payable in three equal annual installments following the first commercial sale of eluforsen, the first of which is due within 90 days following the first commercial sale. The Company is also obligated to make a one-time milestone payment to CFFT of up to $ 3 million (€ 2.6 million) if net sales of eluforsen exceed $ 500 million (€ 437 million) in a calendar year. Lastly, the Company is obligated to make a payment to CFFT of up to approximately $ 6 million (€ 5 million) if it transfers, sells or licenses eluforsen other than for certain clinical or development purposes, or if the Company enters into a change of control transaction prior to commercialization. However, the payment in the previous sentence may be set-off against the $ 16 million milestone payment. Either CFFT or the Company may terminate the agreement for cause, which includes the Company's material failure to achieve certain commercialization and development milestones. The Company's payment obligations survive the termination of the agreement.

### (c) Several liability and guarantees

The Company has issued declarations of joint and several liabilities for debts arising from the actions of Dutch consolidated participating interests, as meant in article 2:403 of the Netherlands Civil Code.

The Company constitutes a tax entity with its Dutch subsidiaries for corporate income tax purposes; the standard conditions prescribe that all companies of the tax entity are jointly and severally liable for the corporate income tax payable.

## 35. Auditor fees

The fees for services provided by our external auditor, Deloitte Accountants B.V., are specified below for each of the financial years indicated:

| | 2018 | 2017 |
|---|---|---|
| | *€ 1,000* | *€ 1,000* |
| Audit fees | 181 | 175 |
| Audit-related fees | 261 | 140 |
| Tax fees | -- | -- |
| All other fees | -- | -- |
| | **442** | **315** |

**Audit fees**
Consist of aggregate fees for professional services provided in connection with the annual audit of our financial statements, procedures on our quarterly financial statements, consultations on accounting matters directly related to the audit, and comfort letters, consents and assistance with and review of documents filed with the SEC.

## Signing of the Annual Report

Leiden, March 28, 2019,

D.A. de Boer

D. Valerio

A.B. Papiernik

A. Lawton

P.R. Baart

J.S.S. Shannon

## Other information

**Independent auditor's report**
Reference is made to the independent auditor's report as included hereinafter.

**Statutory arrangement concerning the appropriation of the result**
In Article 21 of the Company statutory regulations the following has been presented concerning the appropriation of result:

1. The profit is at the free disposal of the General Meeting of Shareholders.

2. The Company may only distribute profits to shareholders and other recipients to distributable profits to the extent that the equity exceeds the paid-up capital plus the reserves required by law.

3. Distribution of profits shall take place after adoption of the annual accounts from which it becomes clear that distribution is permissible.

4. When calculating the distribution of profits shares held by the Company shall be disregarded, unless this shares has been encumbered with usufruct or right of pledge or certificates thereof are issued as a result of which the entitlement to profits accrue to the usufructuary, pledgee or holder of the certificates.

5. Certificates held by the Company or whereon the Company holds limited rights as a result of which the Company is entitled to distribution of profits shall also be disregarded when calculating the distribution of profits.

6. The Company may make interim distributions, only if the requirements in paragraph 2 are met.

# Independent auditor's report

To the Shareholders and the Supervisory Board of ProQR Therapeutics N.V.

## Report on the audit of the financial statements 2018

**Our opinion**
We have audited the accompanying financial statements 2018 of ProQR Therapeutics N.V., based in Leiden, The Netherlands. The financial statements include the consolidated financial statements and the company financial statements.

In our opinion:

- The accompanying consolidated financial statements give a true and fair view of the financial position of ProQR Therapeutics N.V. as at December 31, 2018, and of its result and its cash flows for 2018 in accordance with International Financial Reporting Standards as adopted by the European Union (EU-IFRS) and with Part 9 of Book 2 of the Dutch Civil Code.
- The accompanying company financial statements give a true and fair view of the financial position of ProQR Therapeutics N.V. as at December 31, 2018, and of its result for 2018 in accordance with Part 9 of Book 2 of the Dutch Civil Code.

The consolidated financial statements comprise:

1. The consolidated statement of financial position as at December 31, 2018.
2. The following statements for 2018: the consolidated statement of profit or loss and comprehensive income, consolidated statement of changes in equity and consolidated statement of cash flows.
3. The notes comprising a summary of the significant accounting policies and other explanatory information.

The company financial statements comprise:

1. The company balance sheet as at December 31, 2018.
2. The company income statement for the year ended December 31, 2018.
3. The notes comprising a summary of the accounting policies and other explanatory information.

**Basis for our opinion**
We conducted our audit in accordance with Dutch law, including the Dutch Standards on Auditing. Our responsibilities under those standards are further described in the "Our responsibilities for the audit of the financial statements" section of our report.

We are independent of ProQR Therapeutics N.V. in accordance with the EU Regulation on specific requirements regarding statutory audit of public-interest entities, the Wet toezicht accountantsorganisaties (Wta, Audit firms supervision act), the Verordening inzake de onafhankelijkheid van accountants bij assurance-opdrachten (ViO, Code of Ethics for Professional Accountants, a regulation with respect to independence) and other relevant independence regulations in the Netherlands. Furthermore, we have complied with the Verordening gedrags- en beroepsregels accountants (VGBA, Dutch Code of Ethics).

We believe the audit evidence we have obtained is sufficient and appropriate to provide a basis for our opinion.

**Materiality**
Based on our professional judgement we determined the materiality for the consolidated financial statements as a whole at € 2.000.000. The materiality is based on 5% of total operating costs which is consistent with prior year. We have also taken into account misstatements and/or possible misstatements that in our opinion are material for the users of the financial statements for qualitative reasons.

We agreed with the Supervisory Board that misstatements in excess of € 95.000, which are identified during the audit, would be reported to them, as well as smaller misstatements that in our view must be reported on qualitative grounds.

**Scope of the group audit**
ProQR Therapeutics N.V. is at the head of a group of entities. The financial information of this group is included in the consolidated financial statements of ProQR Therapeutics N.V.

The financial administration for all group entities is centralized in the Netherlands. Consequently, we have centralized our audit approach and we have been able to obtain sufficient and appropriate audit evidence about the group's financial information to provide an opinion about the financial statements.

**Our key audit matters**
Key audit matters are those matters that, in our professional judgement, were of most significance in our audit of the financial statements. We have communicated the key audit matters to the Supervisory Board. The key audit matters are not a comprehensive reflection of all matters discussed.

These matters were addressed in the context of our audit of the financial statements as a whole and in forming our opinion thereon, and we do not provide a separate opinion on these matters. Our key audit matters of 2018 are consistent with those identified during prior year's audit.

*Research and development expenses*

**Description**
The total research and development expenses for the year 2018 amount to € 29.5 million. These research and development expenses consist of payroll costs of employees as well as outsourced research and development activities with third party suppliers. The research and development activities with these suppliers are concluded in master service agreements and statements of work. These outsourced research and development activities are typically performed over a period of time and as a consequence the allocation of expenses to the reporting period is based on the progress of the work which involves (significant) judgement.
The R&D expenses are disclosed in note 16 of the financial statements.

**How the key audit matter was addressed in the audit**
We tested the key control for design and implementation. We decided not to rely on controls and tested the R&D expenses substantively. Our audit procedures included, amongst others, the review of the agreements with suppliers and the related accounting evaluation as well as the timing of expenses recognized. In addition, we tested the progress of projects based on confirmations sent to significant vendors, we performed inquiries of project managers and inspected purchase orders and work orders in order to determine the correct cut-off of R&D expenses and accruals.

**Observation**
The scope and nature of the procedures performed were sufficient and appropriate to address the risks of material misstatement in R&D expenses.

*Significant contracts*

**Description**
ProQR Therapeutics N.V. concluded several significant contracts, such as the above mentioned research and development agreements. These contracts contain terms and conditions that may require complex accounting and/or significant long-term commitments that require disclosure in the financial statements.
The commitments and contingencies are disclosed in note 22 of the financial statements.

**How the key audit matter was addressed in the audit**
We tested the key controls for design and implementation. We decided not to rely on controls and tested the significant contracts substantively. Our audit procedures included, amongst others, the review of the contract register, obtaining external confirmations on significant R&D contracts and the review of the contract terms and related accounting evaluation of the impact on the financial statements including disclosures of the commitments.

**Observation**
The scope and nature of the procedures performed were sufficient and appropriate to address the risk of material misstatements of commitments and contingencies related to the significant contracts.

*Cash and cash equivalents*

**Description**
The total cash and cash equivalents as per December 31, 2018 amount to € 105.6 million. We focused on this area as the cash and cash equivalents are significant to the financial statements. In addition, the availability of sufficient cash and cash equivalents is also important as it provides information of the company's ability to continue as a going concern and fund its planned R&D activities.
Cash and cash equivalents are disclosed in note 11 of the financial statements.

**How the key audit matter was addressed in the audit**
We tested the key controls for design and implementation. We decided not to rely on control and tested the cash and cash equivalents substantively. Our procedures included detailed reconciliations of all bank balances to bank confirmations, recalculating foreign exchange results on these balances and a review of the statements, confirmations and underlying agreements for deposit balances to assess the presentation and disclosure in the financial statements.

**Observation**
The scope and nature of the procedures performed were sufficient and appropriate to address the risks of material misstatement in the cash and cash equivalents.

**REPORT ON THE OTHER INFORMATION INCLUDED IN THE ANNUAL ACCOUNTS**
In addition to the financial statements and our auditor's report thereon, the annual accounts contain other information that consists of:

- Management Board's Report.
- Other Information as required by Part 9 Book 2 of the Dutch Civil Code.

Based on the following procedures performed, we conclude that the other information:

- Is consistent with the financial statements and does not contain material misstatements.
- Contains the information as required by Part 9 of Book 2 of the Dutch Civil Code.

We have read the other information. Based on our knowledge and understanding obtained through our audit of the financial statements or otherwise, we have considered whether the other information contains material misstatements.

By performing these procedures, we comply with the requirements of Part 9 of Book 2 of the Dutch Civil Code and the Dutch Standard 720. The scope of the procedures performed is substantially less than the scope of those performed in our audit of the financial statements.

Management is responsible for the preparation of the other information, including the Management Board's Report in accordance with Part 9 Book 2 of the Dutch Civil Code, and the other information as required by Part 9 Book 2 of the Dutch Civil Code.

**REPORT ON OTHER LEGAL AND REGULATORY REQUIREMENTS**

**Engagement**
We were engaged by the Supervisory Board as auditor of ProQR Therapeutics N.V. starting with the audit for the year 2012 and have operated as statutory auditor ever since that financial year.

**No prohibited non-audit services**
We have not provided prohibited non-audit services as referred to in Article 5(1) of the EU Regulation on specific requirements regarding statutory audit of public-interest entities.

**DESCRIPTION OF RESPONSIBILITIES REGARDING THE FINANCIAL STATEMENTS**

**Responsibilities of management and Supervisory Board for the financial statements**
Management is responsible for the preparation and fair presentation of the financial statements in accordance with EU-IFRS and Part 9 of Book 2 of the Dutch Civil Code. Furthermore, management is responsible for such internal control as management determines is necessary to enable the preparation of the financial statements that are free from material misstatement, whether due to fraud or error.

As part of the preparation of the financial statements, management is responsible for assessing the company's ability to continue as a going concern. Based on the financial reporting frameworks mentioned, management should prepare the financial statements using the going concern basis of accounting unless management either intends to liquidate the company or to cease operations, or has no realistic alternative but to do so.

Management should disclose events and circumstances that may cast significant doubt on the company's ability to continue as a going concern in the financial statements.

The supervisory board is responsible for overseeing the company's financial reporting process.

**Our responsibilities for the audit of the financial statements**
Our objective is to plan and perform the audit assignment in a manner that allows us to obtain sufficient and appropriate audit evidence for our opinion.

Our audit has been performed with a high, but not absolute, level of assurance, which means we may not detect all material errors and fraud during our audit.

Misstatements can arise from fraud or error and are considered material if, individually or in the aggregate, they could reasonably be expected to influence the economic decisions of users taken on the basis of these financial statements. The materiality affects the nature, timing and extent of our audit procedures and the evaluation of the effect of identified misstatements on our opinion.

We have exercised professional judgement and have maintained professional skepticism throughout the audit, in accordance with Dutch Standards on Auditing, ethical requirements and independence requirements. Our audit included e.g.:

- Identifying and assessing the risks of material misstatement of the financial statements, whether due to fraud or error, designing and performing audit procedures responsive to those risks, and obtaining audit evidence that is sufficient and appropriate to provide a basis for our opinion. The risk of not detecting a material misstatement resulting from fraud is higher than for one resulting from error, as fraud may involve collusion, forgery, intentional omissions, misrepresentations, or the override of internal control.
- Obtaining an understanding of internal control relevant to the audit in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the company's internal control.
- Evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates and related disclosures made by management.
- Concluding on the appropriateness of management's use of the going concern basis of accounting, and based on the audit evidence obtained, whether a material uncertainty exists related to events or conditions that may cast significant doubt on the company's ability to continue as a going concern. If we conclude that a material uncertainty exists, we are required to draw attention in our auditor's report to the related disclosures in the financial statements or, if such disclosures are inadequate, to modify our opinion. Our conclusions are based on the audit evidence obtained up to the date of our auditor's report. However, future events or conditions may cause the company to cease to continue as a going concern.
- Evaluating the overall presentation, structure and content of the financial statements, including the disclosures.
- Evaluating whether the financial statements represent the underlying transactions and events in a manner that achieves fair presentation.

Because we are ultimately responsible for the opinion, we are also responsible for directing, supervising and performing the group audit. In this respect we have determined the nature and extent of the audit procedures to be carried out for group entities. Decisive were the size and/or the risk profile of the group entities or operations. On this basis, we selected group entities for which an audit or review had to be carried out on the complete set of financial information or specific items.

We communicate with the supervisory board regarding, among other matters, the planned scope and timing of the audit and significant audit findings, including any significant findings in internal control that we identified during our audit. In this respect we also submit an additional report to the audit committee in accordance with Article 11 of the EU Regulation on specific requirements regarding statutory audit of public-interest entities. The information included in this additional report is consistent with our audit opinion in this auditor's report.

We provide the Supervisory Board with a statement that we have complied with relevant ethical requirements regarding independence, and to communicate with them all relationships and other matters that may reasonably be thought to bear on our independence, and where applicable, related safeguards.

From the matters communicated with the Supervisory Board, we determine the key audit matters: those matters that were of most significance in the audit of the financial statements. We describe these matters in our auditor's report unless law or regulation precludes public disclosure about the matter or when, in extremely rare circumstances, not communicating the matter is in the public interest.

Amsterdam, March 28, 2019

I.A. Buitendijk

# Want to learn more?

Read on about ProQR and our programs
proqr.com

Check out our video "How do ProQR's RNA therapies work?"
proqr.com/rna-video

Follow the latest developments in our pipeline
proqr.com/pipeline

View our complete Annual Report online
proqr.com/ar2018

Download the Thru My Eyes app
thrumyeyes.app

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