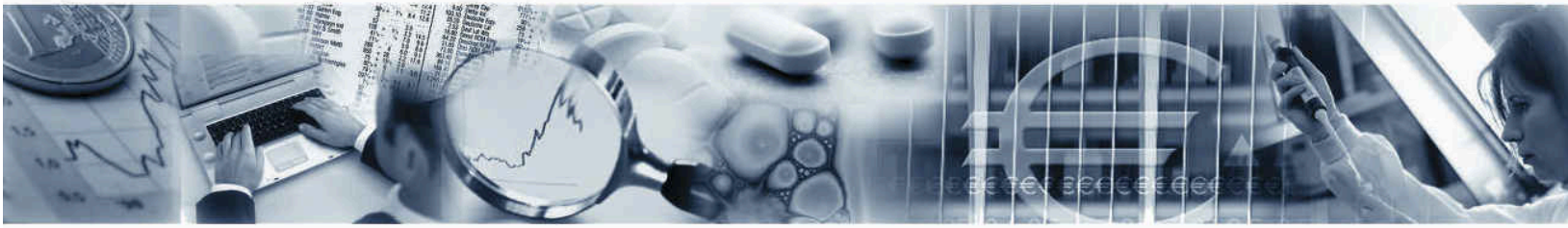

Initiating Coverage Report

ProQR Therapeutics

Focus on Ophthalmology

Chief Research Analyst

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Date: 26 April 2018

Name:	**ProQR Therapeutics**
Country:	**The Netherlands**
Price:	**USD 3.50**
ISIN Code:	**NL0010872495**
Reuters Code:	**PRQR**
Market Cap (USD m):	**109.9**
EV (USD m):	**61.8**
Cash & cash eq. (EUR m):	**48.1**
Shares outstanding (m):	**31.9**
Volume:	**90,730**
Free float:	**100%**
52-week Range:	**2.75-6.90**

EUR million	2015A	2016A	2017A
Total Revenues	3.235	1.828	1.495
Net (Loss)/Profit	(20.831)	(39.119)	(43.524)
Net (loss)/profit ps (cents)	(0.89)	(1.67)	(1.72)
R&D costs	23.401	31.923	31.153
Cash increase/(decrease)	(23.936)	(36.403)	(8.432)
Cash and marketable sec.	94.865	59.200	48.099

Executive Summary

Executive Summary

- ProQR Therapeutics is an innovative biopharma company that is developing RNA-based therapeutics for the treatment of severe genetic disorders such as cystic fibrosis, Leber's congenital amaurosis Type 10 and dystrophic epidermolysis bullosa. The company's growing pipeline is based on its proprietary technology platform of RNA technologies.

- Its lead program is eluforsen (formerly QR-010), which is currently in Phase IB for cystic fibrosis, is a first-in-class RNA-based oligonucleotide that is designed to address the underlying cause of the disease by targeting the mRNA defect encoded by the Delta F508 mutation in the CFTR gene of patients with Cystic Fibrosis (CF). In July 2016, eluforsen received a Fast Track designation by the US Food and Drug Administration (FDA). Drugs that are under development for serious conditions and have the potential to fulfill an unmet medical need can receive this designation. Eluforsen is expected to advance into a phase II study in 2018. We believe the company will aim for a partnership with big pharma in order to focus on its programs in retinal dystrophy.

- ProQR's second program QR-110 is earlier in development than eluforsen, but we feel that it is becoming more important for the company. QR-110 is a therapy designed to address the underlying cause of Leber's congenital amaurosis (LCA) 10. Despite eluforsen being further clinically validated than QR-110, the CF market has become notably more competitive during eluforsen's development, inclining ProQR to focus ton its strong ophthalmic pipeline, especially given how amenable such indications are to local drug administration. A Phase 1b/2 trial for QR-110 was initiated in 2017Q4, and we expect initial results in 2018. Given the recent success from a program in LCA 2 by Spark Therapeutics (ONCE, NC), we believe potential positive results from the 12-month readout could set the path for registration.

- The Company's current cash position is EUR 48.1 million including a successful raise of USD 20 million end of 2017. This should be sufficient to carry out the further development of its pipeline till mid 2019. Net cash used in operating activities during 2017 was EUR 35.0 million compared to EUR 34.2 million for 2016.

- **Based on NPV based valuation, we believe that ProQR is substantially undervalued at the current share price of USD 3.50. Using our valuation model and taking into account a potential partnership with eluforsen and future revenues of QR-110, the company's current total value should be USD 350-400 million, or USD 11.00-12.50 per share. This represents a substantial upside from the current share price.**

Company Profile

ProQR Therapeutics was founded in May 2012 in Leiden, the Netherlands with the goal of developing a treatment for cystic fibrosis. Nowadays, ProQR Therapeutics has grown to be an innovative biopharma company that is developing RNA-based therapeutics for the treatment of severe genetic disorders such as cystic fibrosis, Leber's congenital amaurosis Type 10 and dystrophic epidermolysis bullosa. The company's growing pipeline is based on its proprietary technology platform of RNA technologies. Since September 2014 the company is listed on NASDAQ under ticker PRQR. Currently, there are over 140 people that work for ProQR worldwide.

RNA Technology Platform

Unlike other approaches in the RNA therapeutics field, such as RNAi and antisense, ProQR's RNA approach aims to treat genetic disorders by targeting the defective mRNA with specifically designed single-stranded RNA-based oligonucleotides to restore functional protein. The oligonucleotides are highly specific for the targets and are chemically modified for stability and uptake. This RNA approach allows the company to develop novel therapies for genetic disorders that are currently untreatable or have limited effective treatment options. In the CF field, which is the company's initial focus, Eluforsen is designed to target the Delta F508 mutation, resulting in the production of functional CFTR protein. Currently, ProQR is the only company pursuing this RNA approach for CF patients. Next to CF, the company is also developing an RNA treatment for Leber's congenital amaurosis Type 10, or LCA 10, the leading genetic cause of blindness in childhood and a therapy for the dystrophic form of epidermolysis bullosa, a highly debilitating skin disease. Besides, we think that ProQR's RNA technologies can potentially be used to treat a broad range of other severe genetic diseases with high unmet medical need. To date the company has identified more than 100 potential targets.

Business Strategy

Key elements of ProQR's strategy are:

- Rapidly advance eluforsen for the treatment of CF. Its lead product candidate, eluforsen, has generated compelling data in pre-clinical studies and an exploratory proof of concept clinical study using an important biomarker for CFTR activity. A second Phase Ib safety and tolerability study was concluded with positive topline results. ProQR is also studying applications of its RNA technologies for mutations other than Delta F508 that could potentially be used to treat an additional 10% of CF patients.

- Utilize its proprietary RNA technologies and know-how to develop additional product candidates targeting genetic diseases with high unmet medical need. The company wants to develop a product pipeline targeting severe genetic diseases with no or limited effective treatments caused by mutations that can be treated with the RNA technologies. ProQR has identified approximately 100 potential target indications. As the first non-CF therapeutic program, the company moved its QR-110 program into clinical development in 2017H1 for the treatment of patients with the most common mutation causing Leber's congenital amaurosis Type 10, the leading genetic cause of blindness in childhood. A third program, QR-313, moved into development during 2016. It targets dystrophic epidermolysis bullosa, a severe genetic skin disease of which some forms are associated with a limited life-expectancy and a low quality-of-life.

- ProQR is currently designing a 12-week Phase II safety and efficacy study of eluforsen in CF subjects with the F508del mutation. The trial is expected to be conducted at clinical centers in North America, EU and other countries. The Company plans to initiate the trial in 2018 subject to a partnership with big pharma.

- Consider collaborative partnerships to develop and commercialize its proprietary RNA technologies or programs in specific indications outside of CF. The company considers collaborative partnerships with pharmaceutical companies and others to leverage its core technologies in therapeutic areas beyond CF depending on the attractiveness of the opportunities. These partnerships may provide further validation of the RNA technologies and funding to advance our product candidates and access to development, manufacturing and commercial expertise and capabilities.

Technology Platform: RNA Repair

Genes are the specific sequences of DNA that provide the blueprint used by the human body's cells to make proteins, which are enzymes or other large molecules in cells that serve a functional purpose. Each gene consists of a specific sequence of nucleotides that leads to the production of a specific protein. The gene's coding DNA sequence is transcribed into mRNA, which is subsequently translated into the specific protein. A mutation, or defect, in a specific gene can result in the transcription of abnormal mRNA, which then can produce a defective, misfolded or truncated protein that is unable to carry out its normal function. Unlike other approaches in the RNA therapeutics field, such as RNAi and antisense, ProQR's RNA repair approach aims to treat genetic disorders by repairing the basic defect in the mRNA, thus resulting in fully-functional, wild-type protein. This approach employs single-stranded RNA-based oligonucleotides, which act as guide sequences to repair the targeted abnormal mRNA. The repaired mRNA then acts as a template to generate functional protein. We believe this RNA repair approach will allow the company to develop novel therapies for genetic disorders that are currently untreatable or have limited effective treatment options.

Source: ProQR Therapeutics

In the CF field, eluforsen is designed to bind the defective mRNA with the F508del mutation, resulting in functional CFTR protein. We believe we are the only company currently pursuing this RNA repair approach for CF patients.

Axiomer®: The Next Generation in RNA Technology

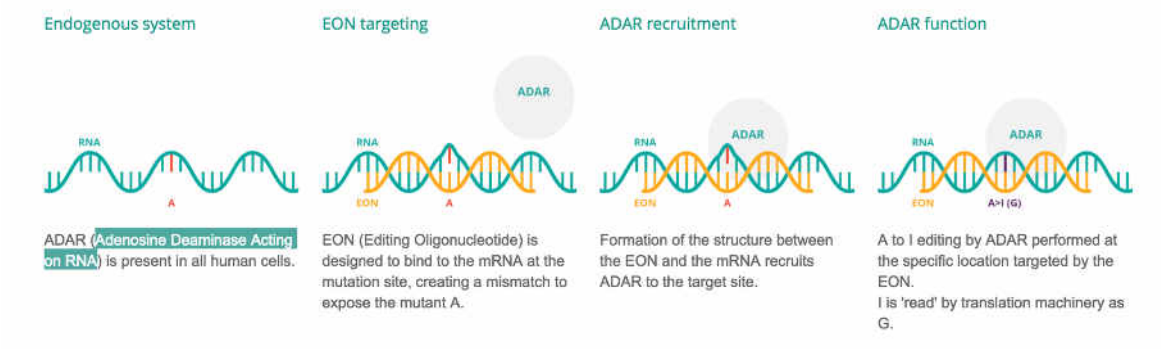
ProQR has discovered and developed a next-generation RNA technology called Axiomer®, which could potentially yield a new class of medicines for genetic diseases. Axiomer's editing oligonucleotides, or EONs, are designed to recruit endogenous Adenosine Deaminases Acting on RNA, or ADAR, enzyme, and direct ADAR to make a change in the RNA at the desired location. ADAR can modify an Adenosine in the RNA into an Inosine, which is translated in the protein synthesis as a Guanine. The Axiomer platform may be applicable to more than 20,000 disease-causing mutations.

Antisense oligonucleotides (AONs) have been explored and developed as therapeutics for the last few decades. AONs are designed to inhibit the expression of a target RNA, or adjust the splicing pattern of an RNA. Scientists at ProQR have invented a new way to use oligonucleotides to edit single nucleotides in the RNA. These Editing Oligonucleotides (EONs) make specific A-to-I changes to RNA (ADAR) to reverse the underlying cause of currently untreatable diseases. ProQR specifically design EONs that attract the cells own RNA editing machinery and direct it to a mutation site, where it repairs the RNA and thereby allows a functional protein to be produced.

The Importance of ADAR

To target a specific disease, ProQR's EONs are designed to bind only to the specific, mutated site in the RNA. Special structures in the EON attract the endogenous ADAR complex tot he site where the complex edits the targeted 'A' to an 'I'. The EONs are short single stranded RNA molecules that are chemically modified to provide them with ideal drug-like properties for efficacy and uptake

into cells. There are over 20,000 disease causing mutations that can be reversed by A to I ediging. The vast majority of these diseases are currently untreatable.



Source: ProQR Therapeutics

Beginning of this year, ProQR announced that it has entered into a research collaboration agreement with Galapagos N.V. (Euronext & NASDAQ:GLPG). Under the agreement the two companies will work together to discover novel Axiomer EONs against fibrosis targets selected by Galapagos. The targets that will be pursued in the collaboration and financial details about the collaboration are not disclosed.

Pipeline: Focus on Rare Genetic Disorders

ProQR's current pipeline consists of programs in cystic fibrosis, ophthalmology and dermatology. For cystic fibrosis, or CF, a severe genetic disease that affects approximately 77,000 people in the United States, European Union, Canada and Australia, the company is developing eluforsen for the F508del mutation, which has completed two clinical trials with positive top-line data. Besides, ProQR has a discovery pipeline for other genetic mutations causing CF. For ophthalmology, the company is developing QR-110 for Leber's congenital amaurosis type 10, or LCA10, which is currently studying in a Phase I/II safety and efficacy clinical trial, QRX-421 for the ophthalmic manifestations of Usher syndrome due to exon 13 mutations in preclinical development, QRX-411 for the ophthalmic manifestations of Usher syndrome due to the PE-40 mutation in preclinical development, QRX-1011 for Stargardt's disease due to an exon 39 splicing mutation in the ABCA4 gene in discovery stage and QRX-504 for Fuchs endothelial corneal dystrophy in discovery stage. In dermatology, ProQR is developing QR-313 in preclinical studies for the exon 73 mutation leading to dystrophic epidermolysis bullosa, or DEB, a severe genetic blistering skin disease.

Eluforsen (formerly QR-010) in CF

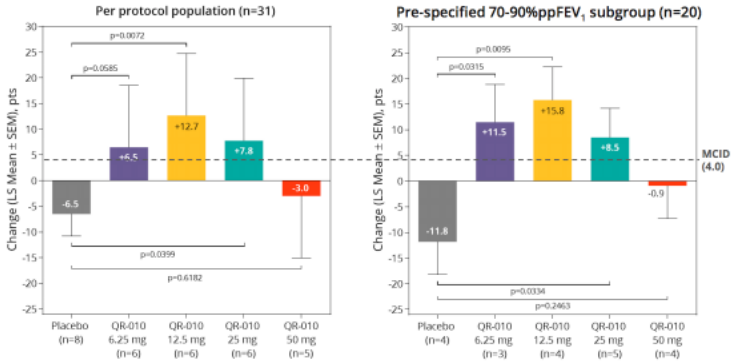
ProQR's lead product candidate for CF, eluforsen, is a single stranded RNA oligonucleotide designed to restore CFTR function in patients suffering from the F508del mutation. Eluforsen is self-administered via an eFlow Nebulizer manufactured by PARI Pharma GmbH. In preclinical studies, eluforsen was observed to restore CFTR function in three cellular models and two animal models. Eluforsen was observed in in vitro and in vivo experiments to be able to diffuse through the CF mucous. Eluforsen has been granted orphan drug designation by the European Commission and Food and Drug Administration, or FDA, for the treatment of CF caused by the F508del mutation. Eluforsen has also received fast track designation from the FDA for the treatment of CF caused by the F508del mutation. The eluforsen project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 633545. The company intends to seek a strategic partner for further development of eluforsen for CF.

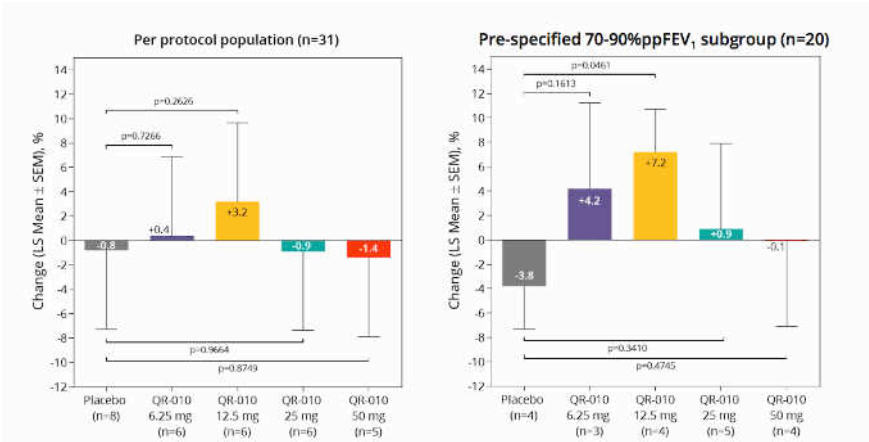
ProQR conducted two clinical trials of eluforsen in parallel. PQ-010-001 was a Phase Ib randomized, double-blind, placebo-controlled, dose-escalation 28-day study with follow-up that enrolled 70 patients with baseline forced expiratory volume in one second, or FEV1, of at least 70% in 23 centers in North America and Europe, of which 34 subjects were included in the multiple ascending dose cohorts. This study evaluated the safety, tolerability and, as a secondary endpoint, pharmacokinetics of single and multiple ascending doses of inhaled eluforsen in CF patients homozygous for the F508del mutation. Exploratory efficacy endpoints included sweat chloride, weight gain, CFQ-R Respiratory Symptom Score, or CFQ-R RSS, and lung function as measured by FEV1. In the single dose cohorts, patients received a single dose of eluforsen of 6.25 mg, 12.5 mg, 25 mg or 50 mg or placebo. In the multiple dose cohorts, patients received over a period of four weeks 12 doses of eluforsen of 6.25 mg, 12.5 mg, 25 mg or 50 mg or placebo.

Study PQ-010-002 is a proof-of-concept trial evaluating the effect of topical administration of eluforsen in the nose on the nasal potential difference (NPD), a biomarker of CFTR function. This trial opened for enrollment in September 2015 and was completed in September 2016. Topline results were reported at the North American CF Conference in October 2016. In the per-protocol population of subjects homozygous for the Delta F508 mutation meeting the pre-specified inclusion criteria (n=7), the average change from baseline in NPD at day 26 was statistically significant, -4.1 mV (p=0.0389). These results are in the same range as Kalydeco, an approved product developed by Vertex Pharmaceuticals (NASDAQ:VRTX) for a different subset of CF patients. Studies showed that the strong effect on NPD translated to a strong increase in FEV1. Lumacaftor, another product candidate for CF patients developed by Vertex did not show an effect in NPD and this translated to no effect on FEV1 in later studies. The findings on NPD for eluforsen were supported by a change in sodium channel activity (specifically, a measure called max basal potential difference, or PD) and other sensitivity analyses of the NPD measurements, all pointing to strong evidence of restoration of CFTR activity. In subjects compound heterozygous for the Delta F508 mutation, the average change from baseline in NPD was not significantly different at day 26. Eluforsen administered via the intranasal route was observed to be well tolerated.

Study PQ-010-001 is a Phase Ib safety and tolerability trial. This trial opened for enrollment in June 2015 and completed enrollment in August 2017. The study enrolled a total of 64 adult Delta F508del patients that have a relatively good lung function (ppFEV1 >70%). A total of 4 dose levels were studied: 6.25, 12.5, 25 and 50mg of eluforsen in solution per dose administered via inhalation. The study design consisted of 8 cohorts of 8 patients for a total of 64 patients. In each cohort, 6 patients received eluforsen and 2 patients received placebo. In cohorts 1-4, a single dose of eluforsen was administered, and in cohorts 5-8 twelve doses of eluforsen were administered over a 4-week period. Patients included in the study were adult patients with mild CF disease with a baseline predicted FEV1 value above 70%. n this trial Eluforsen was observed to be safe and well-tolerated across all doses, with an overall safety profile similar to placebo. There were no serious adverse events related to treatment. After inhaled administration in some dose groups, eluforsen

was detected in the blood. Subjects who received eluforsen in the 6.25, 12.5 and 25 mg multiple dose groups reported fewer respiratory symptoms after 4 weeks of treatment as measured by the increased CFQ-R RSS, with mean improvements of 13.0, 19.2 and 14.3 points, respectively, compared to placebo. The effect was more pronounced in the pre-defined subgroup of subjects with a lower lung function at the start of the study (baseline ppFEV$_1$ 70-90%) with a mean increase of up to 27.5 points compared to placebo. These improvements exceeded the minimal clinically important difference (MCID) of 4.0 points. A supportive trend of improved lung function was observed in the same multiple dose groups, as measured by mean absolute change in ppFEV$_1$ compared to placebo. The trend was stronger in the subgroup of subjects with a lower lung function at baseline.





PQ-010-003 is currently planned as a Phase II multicenter, randomized, double-blind, placebo-controlled 12-week trial to evaluate the safety, efficacy, and pharmacokinetics of eluforsen in cystic fibrosis subjects with the Delta F508 mutation. The trial will be conducted at clinical centers in North America, EU and possibly other countries. Pending partnership discussion, the company anticipates to begin recruitment for this trial in 2018.

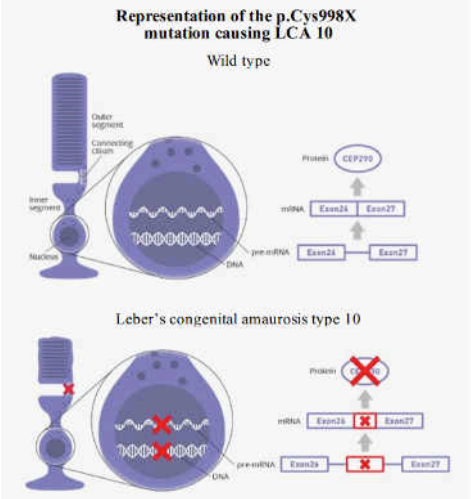
To achieve broad distribution to CF-affected organs, eluforsen is delivered through inhalation by means of a small handheld nebulizer, a method of drug delivery used to administer medication in the form of a mist inhaled into the lungs. On October 8, 2014 ProQR entered into an agreement with PARI Pharma GmbH, pursuant to which the company is granted an exclusive license to the use of PARI's eFlow technology for the administration of oligonucleotide-based drugs in the Delta F508 mutation in cystic fibrosis. The nebulizer device rapidly and efficiently processes a therapeutic agent through the microscopic holes of a mesh and creates a mist to provide rapid and consistent delivery to the lungs. Commercially-available nebulizers are currently used for other CF therapies and in other clinical studies involving inhaled oligonucleotides.

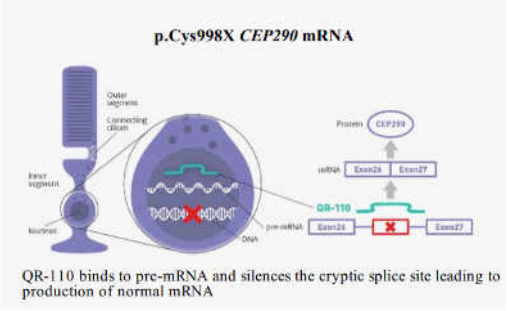
QR-110 in LCA 10

Leber's Congenital Amaurosis (LCA) is the most common genetic cause of blindness in childhood. ProQR believes that the p.Cys998X mutation in the CEP290 (Centrosomal protein of 290 kDa) gene is the most prevalent mutation which generally accounts for the most severe disease phenotype (LCA 10). Patients affected by this mutation typically lose sight in the first years of life. In LCA 10 patients, this mutation leads to significant decrease in CEP290 protein within the photoreceptor cells in the retina. Clinical features of CEP290-mediated LCA include loss of vision, involuntary eye movement or nystagmus, abnormalities of pupil reactions and no detectable photoreceptor electrical signals on electroretinography (ERG). End of last year, Spark Therapeutics (NASDAQ: ONCE) received approval from the FDA for its gene therapy Luxturna for LCA Type 2. However,

several patients in the pivotal trial got severe negative complication from the subretinal injection. There are other approaches in pre-clinical development for the p.Cys998X mutation that target the disease at the DNA level.

ProQR's lead product candidate in the LCA 10 space, QR-110, is a first-in-class single stranded RNA oligonucleotide of 17 nucleotides long. It is designed to treat the disease by binding to the pre-mRNA and thereby silencing the cryptic splice site caused by the p.Cys998X mutation. The splicing machinery can thus splice the pre-mRNA correctly resulting in normal mRNA and probably the production of full-length functional wild-type CEP290 protein. The intended route of delivery is through intravitreal injection. QR-110 was granted orphan drug designation (ODD) from both the FDA and the European Medicines Agency (EMA). In April 2017, the company announced that it initiated a Phase I/II clinical trial This trial is an open label trial evaluating multiple doses of QR-110 at different dose levels. Eligible subjects will be LCA 10 patients that are homozygous or compound heterozygous for the p.Cys998X mutation. The primary objective will be to evaluate the safety and tolerability of QR-110 administered via intravitreal injection in subjects with LCA 10 due to the p.Cys998X mutation. Secondary objectives will include the assessment of pharmacokinetics and efficacy as assessed by specialized ophthalmic tests. The first patient was dosed in November and in April eight out of twelve patients were enrolled.





Source: ProQR Therapeutics

Interim safety and efficacy trial results from the majority of patients after 6 months of treatment are expected in 2018H2, full 12 month treatment data from all patients are expected in 2019.

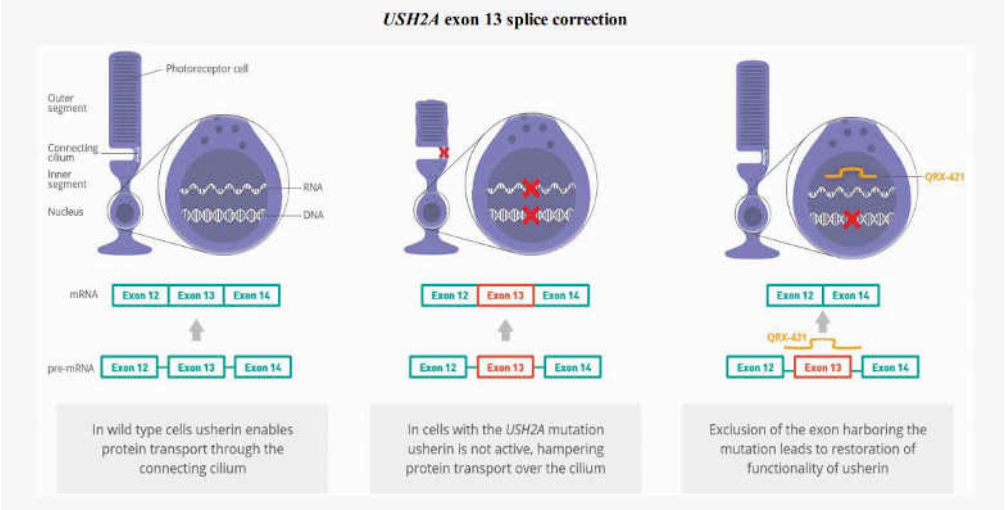
In May 2017, ProQR received Fast Track designation from the FDA. Fast Track designation is granted by the FDA to drugs that are under development for serious conditions and have the potential to fulfill an unmet medical need. It was established with the intention to bring promising drugs to patients sooner by facilitating the development with more frequent FDA interactions and expediting the review process.

QRX-421 and QRX-411 in Usher Syndrome

Usher syndrome is an extremely rare genetic disorder caused by a mutation in any one of at least 11 genes resulting in a combination of hearing loss and visual impairment. 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 vision and moderate to severe deafness. To date, there are no treatments approved or products in clinical development that treat the vision loss associated with the disease. Usher syndrome Type II is one of the most common forms of Usher syndrome and is caused by mutations in the USH2A gene. USH2 is most commonly caused by

mutations in a gene in the DNA called the USH2A gene. This gene is responsible for the formation of the usherin protein. The mutation results in a lack of (functional) usherin protein and disrupts a process called photo transduction in the light detecting cells (rods and cones) in the retina causing RP.

QR-421a is an experimental medicine that is designed to treat retinitis pigmentosa (RP) associated with Usher syndrome type 2 caused by mutations in exon 13 of the USH2A gene. By restoring functional usherin protein expression, QR-421a aims to treat the underlying cause of RP associated with the disease. QR-421a has shown promising results in the laboratory but has not been tested in humans yet. QRX-411 is a first-in-class RNA-based oligonucleotide designed to address the underlying cause of Usher syndrome due to the c.7595-2144A>G mutation in the USH2A gene. In July 2017, ProQR received orphan drug designation from the FDA and EMA frot he treatment of RP, including Usher Syndrome. People with Usher syndrome represent roughly one-sixth of people with RP.



Source: ProQR Therapeutics

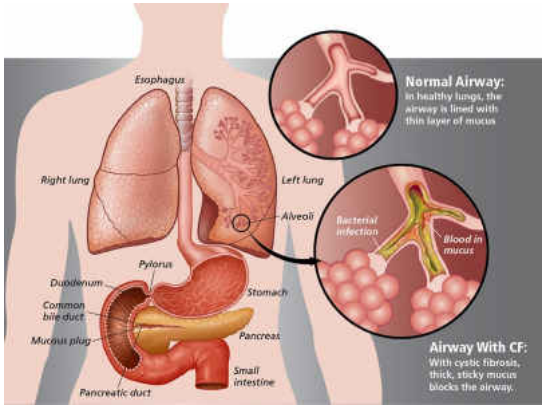
In February, the company entered into a partnership to develop QR-421a for Usher Syndrome with Foundation Fighting Blindness. The Foundation Fighting Blindness was established in 1971 and

has raised more than USD 725 million for research on preventing, treating and curing blindness caused by inherited retinal diseases. Under the agreement, Foundation Fighting Blindness will provide up to USD 7.5 million in funding to ProQR for the preclinical and clinical development of QR-421a, which is expected to advance towards the clinic in 2018, and safety and efficacy results from the Phase I/II trial in Usher syndrome patients are expected in 2019.

ProQR is also developing QRX-1011 for Stargards disease due to an exon 39 splicing mutation in ABCA4 and QRX-504 for Fuchs' endothelial corneal dystrophy 3. Both programs are in the optimization phase, which is the last stage in discovery. Once optimized, the company intends to advance these molecules into pre-clinical development.

Cystic Fibrosis: Lethal Genetic Disorder

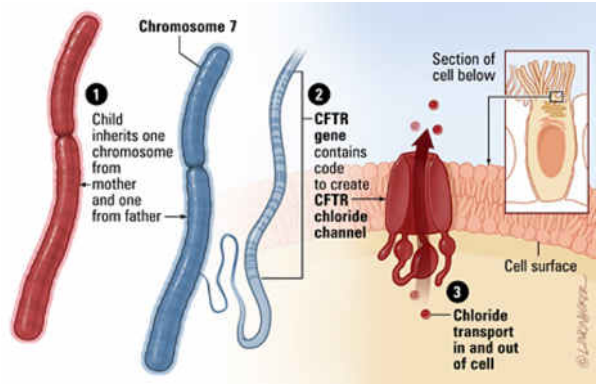
Cystic fibrosis (CF) is an inherited genetic disorder that affects mostly the lungs, but also the pancreas, liver, kidneys and intestine. Long-term issues include difficulty breathing and coughing up mucus as a result of frequent lung infections. CF affects the cells that produce mucus, sweat and digestive juices. These secreted fluids are normally thin and slippery. But in people with cystic fibrosis, a defective gene causes the secretions to become sticky and thick. Instead of acting as a lubricant, the secretions plug up tubes, ducts and passageways, especially in the lungs and pancreas. CF is the most common fatal inherited disease in the western world and affects an estimated 70,000 to 100,000 patients worldwide. There is no cure for CF. CF patients require lifelong treatment with multiple daily medications, frequent hospitalizations and ultimately lung transplants, which can extend life for five years on average.



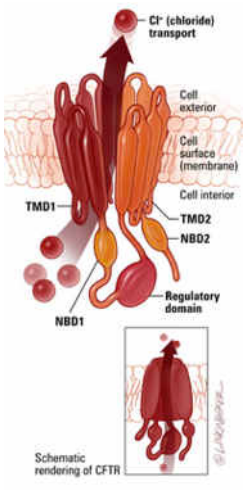
Scientific Background Cystic Fibrosis and CFTR protein

Construction and placement of the CFTR protein in the cell membrane occurs in distinct phases. Located on the long (q) arm of chromosome 7 at position 31.2, the *CFTR* gene is comprised of 27 exons that encode its genetic sequence. An exon is a portion of a DNA that contains the code for

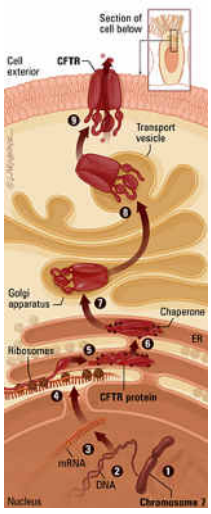
a protein structure. The CFTR gene is transcribed into a single strand of RNA within the cell nucleus; regions that are not needed to make the protein are spliced out, producing the final messenger RNA (mRNA).



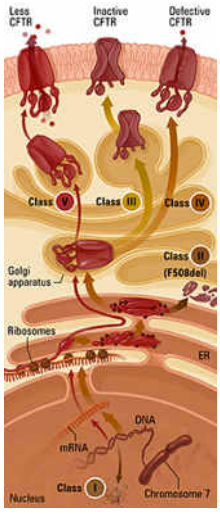
Cystic fibrosis is caused by mutations in the CFTR gene



CFTR Channel



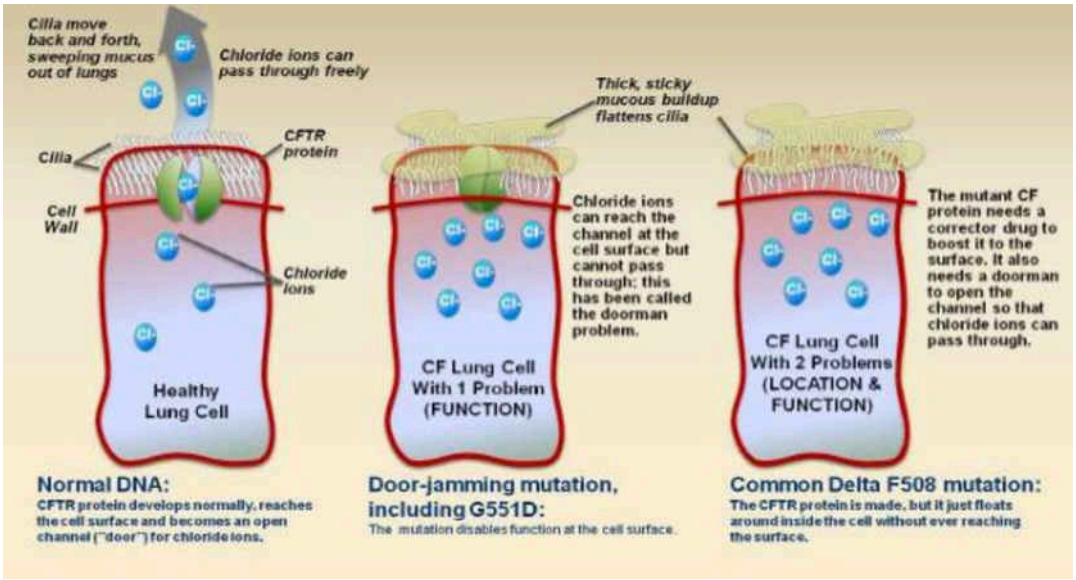
Coding, construction and placement of the CFTR protein



CFTR Channel mutations

The mRNA is translated into protein by ribosomes after moving from the nucleus to the endoplasmic reticulum, or ER. A number of proteins called chaperones facilitate folding of the new CFTR protein and its transfer through the ER. CFTR is then further processed in the Golgi apparatus where sugars are added, and then sent to the apical surface of the cells.

CF is caused by mutations in the CFTR protein. The CFTR protein channel regulates the movement of specific ions in and out of the cells of organs like the lungs, pancreas and gastrointestinal tract. Through regulation of these ions, the amount of salts in the fluid both inside and outside the cell remains balanced. In CF patients, however, the CFTR protein is defective and cannot perform its normal function of transporting ions across the cell membrane, and this results in an environment characterized by thick mucus in vital organs such as the lung, the pancreas and the gastrointestinal tract. The figure below illustrates a defective CFTR protein hampering the efflux of chloride in lung epithelial cells.

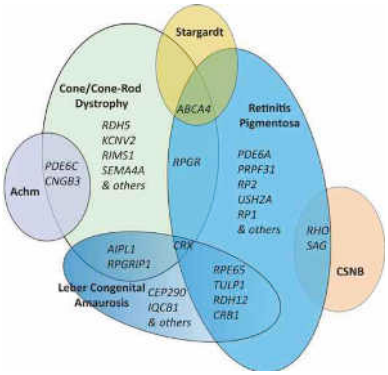


Source: J Cyst Fibros. 2012 May 11 (3): 237-45

Retinal Dystrophies: Rare Degenerative Eye Diseases

Retinal dystrophies (RDs) are degenerative diseases of the retina which have marked clinical and genetic heterogeneity. Common presentations among these disorders include night or colour blindness, tunnel vision and subsequent progression to complete blindness. The known causative disease genes have a variety of developmental and functional roles with mutations in more than 120 genes shown to be responsible for the phenotypes. In addition, mutations within the same gene have been shown to cause different disease phenotypes, even amongst affected individuals within the same family highlighting further levels of complexity. Retinal dystrophies (RDs) are a group of conditions that have a range of clinical manifestations which are estimated to affect as many as 1 in 4,000 individuals. Cases may be syndromic or non-syndromic. Vision impairment may vary from poor peripheral or night vision to complete blindness, and severity usually increases with age. Cases may be familial with autosomal recessive, autosomal dominant or X-linked modes of inheritance described, with sporadic cases also observed. Due to the high genetic heterogeneity underlying these disorders, prioritisation in examining the >120 genes known to be associated with the inherited RDs is challenging. This has led to a lack of readily available testing in many countries for examination of all associated genes in a cost-effective and timely manner.

Genetic heterogeneity in retinal dystrophies.



RDs involving the simultaneous degradation of both rod and cone photoreceptor functions are termed generalized RDs. The majority of cases present with progressive, often severe, deterioration of vision. The most common non-syndromic generalised RD is Leber Congenital Amaurosis (LCA).

Leber Congenital Amaurosis (LCA)

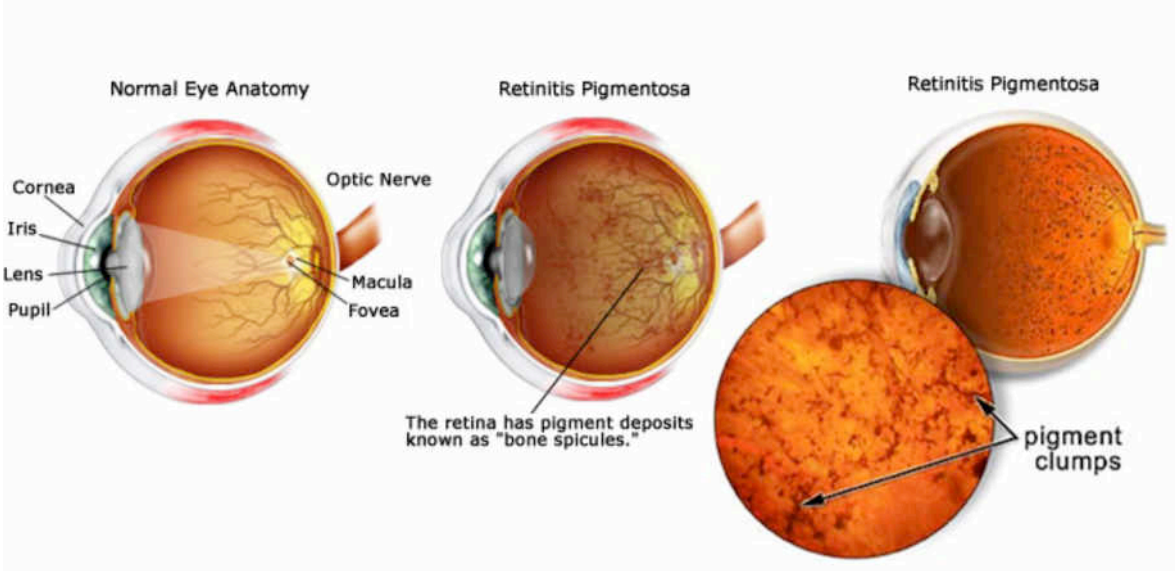
LCA is a rare inherited eye disease Leber's congenital amaurosis (LCA) is a rare inherited eye disease that appears at birth or in the first few months of life, and affects around 1 in 80,000 of the population. The term congenital refers to a condition present from birth (not acquired) and amaurosis refers to a loss of vision *not* associated with a lesion. However, beyond these general descriptions, the presentation of LCA can vary, because it is associated with multiple genes.

LCA is typically characterized by nystagmus, sluggish or absent pupillary responses, and severe vision loss or blindness. There are currently 18 types of LCA recognized. The gene CEP290 is associated with type 10 LCA (about 12% of all cases). The gene CEP290 is a centrosomal protein that plays an important role in centrosome and cilia development. This gene is vital in the formation of the primary cilium, a small antenna-like projections of the cell membrane that plays an important role in the photoreceptors at the back of the retina (which detect light and color) and in the kidney, brain, and many other organs of the body. Knocking down levels of the CEP290 gene transcript resulted in dramatic suppression of ciliogenesis in retinal pigment epithelial cells in culture, proving just how important CEP290 is to cilia formation.

Usher syndrome

The most common clinical manifestation of RD is retinitis pigmentosa (RP). RP is a progressive non-syndromic rod-cone disease and has high levels of clinical and genetic heterogeneity. People with Usher syndrome represent roughly one-sixth of people with retinitis pigmentosa. Usher syndrome is responsible for the majority of deaf-blindness. The word *syndrome* means that multiple

symptoms occur together, in this case, deafness and blindness. It occurs in roughly 1 person in 23,000 in the United States. The progressive blindness of Usher syndrome results from retinitis pigmentosa. The photoreceptor cells usually start to degenerate from the outer periphery to the center of the retina, including the macula. The degeneration is usually first noticed as night blindness (nyctalopia); peripheral vision is gradually lost, restricting the visual field (tunnel vision), which generally progresses to complete blindness. The qualifier 'pigmentosa' reflects the fact that clumps of pigment may be visible by an ophthalmoscope in advanced stages of degeneration. Although Usher syndrome has been classified clinically in several ways, the prevailing approach is to classify it into three clinical sub-types called Usher I, II and III in order of decreasing severity of deafness. Usher I and II are the more common forms.



Source: National Eye Institute

Stargardt Disease

Stargardt disease is the most common inherited retinal disease. It usually has an autosomal recessive inheritance caused by mutations in the ABCA4 gene. Rarely it has an autosomal dominant inheritance due to defects with ELOVL4 or PROM1 genes. It is characterised by macular degeneration that begins in childhood, adolescence or adulthood, resulting in progressive loss of vision. Stargardt disease remains an incurable condition. Current therapeutic options include photoprotection and low-vision aids. Pharmacological slow-down of the visual cycle and gene therapy represent prospects of long-term visual rescue.

SWOT Analysis

Strengths	Weaknesses
Strong management with extensive relevant technical, commercial and financial expertise	Operating losses cumulating year-on-year
Growing revenues from existing products provides source of cash flow	Relatively low market value makes its more challenging to be on investor's radar.
Rare diseases provides quicker time to market	Competition with established players

Opportunities	Threats
	Delay in trials and filing with its programs in CF and ophthamology
Increasing interest from big Pharma following deal size in recent years	Increasing competition from larger companies
Large growing markets	Failure to sign partnerships in key markets
High unmet medical needs rare diseases	

Patent Position

ProQR Therapeutics has built a broad IP portfolio and manages several families of patents. Worldwide the company owns 18 patent families and operates 6 licenses from academia (MGH, INSERM, Radboud University and Leiden University).

With regard to eluforsen, ProQR owns an international patent application filed under the Patent Cooperation Treaty, or PCT, relating to certain aspects of its RNA repair technology platform, including method of use claims relating to the use of certain single stranded oligonucleotides, particularly modified RNA oligonucleotides, for making a change in the sequence of a target RNA molecule in a living cell, as well as composition of matter claims relating to eluforsen. An international patent application filed under the PCT permits a patent applicant to delay the filing and substantive examination of patent applications, and the associated cost, in a number of countries or regions, including commercially significant countries or regions, for a period of time up to the expiration of the international patent application, which, depending upon the country or region, can be up to 30 or 31 months from the earliest priority date claimed by international patent application. International patent applications, however, do not issue as patents. Rather, a patent applicant wishing to obtain patent rights in specific countries or regions must file patent applications in those countries or regions before expiration of the international patent application.

In May 2012, ProQR entered into an exclusive license agreement with Massachusetts General Hospital, or MGH, to obtain rights to a patent family with claims directed to an alternative RNA repair platform that uses an RNA oligonucleotide complex rather than a single stranded oligonucleotide. This patent family includes an issued U.S. patent with a composition of matter claim directed to an RNA oligonucleotide complex containing two specific oligonucleotide

sequences for modulating the expression or activity of a CFTR gene product, and an allowed U.S. patent application with method of use claims relating to the treatment of a symptom of cystic fibrosis in a subject by administering to the subject an RNA oligonucleotide complex comprising two oligonucleotides, as well as a composition of matter claim directed to a specific RNA complex for modulating the activity of a CFTR gene product.

With regard to the LCA Program, in April 2014, ProQR entered into an exclusive license agreement with the Radboud University Medical Center, Nijmegen, the Netherlands, to obtain rights in a patent family with composition of matters claims directed to certain antisense oligonucleotides for treating LCA and method of use claims relating to modulation of the splicing of the CEP290 gene product.

In short, the patents protect these and the other programs and technology at ProQR for years to come:

- Eluforsen for F508del through 2033
- QR-110 for LCA10 through 2036
- QR-313 for DEB exon 73 through 2036
- QR-411 for Usher PE-40 through 2037
- QR-421a for Usher exon 13 through 2037
- Axiomer® platform technology through 2037

Financials

For 2017FY, ProQR reported a net loss of EUR 43.7 million compared to a net loss of EUR 39.1 million in 2016. Expenses for the period totaled to EUR 42 million (2016: EUR 41.4 million). Research and development costs for the year ended December 31, 2017 were EUR 31.2 million, compared to EUR 31.9 million for the same period in 2016. General and administrative costs for the year ended December 31, 2017 were EUR 10.8 million, compared to EUR 9.5 million for 2016.

At the end of 2017, ProQR held cash and cash equivalents of EUR 48.1 million, compared to EUR 59.2 million at December 31, 2016. Net cash used in operating activities during 2017 was EUR 35.0 million, compared to EUR 34.2 million in 2016. In November, the Company completed a USD 20.0 million registered direct offering of 1.4 million ordinary shares at an issue price of USD 3.25 per share with institutional investors. Proceeds from these offerings along with existing cash on the balance sheet, are expected to fund operations into 2019H2.

Profit & Loss Statement

EUR mln	2016A	2017A
Revenues	1.828	1.495
R&D Costs	(31.923)	(31.153)
G&A costs	(9.478)	(10.840)
Operating result	(39.573)	(40.498)
Finance expenses	0.470	(3.175)
Other	(0.016)	0.151
Net Result	(39.119)	(43.524)

Consolidated statement of cash flows

EUR mln	2016A (12 months)	2017-A (12 months)
Cash flow from operating activities	(34.221)	(34.951)
Cash flow from investing activities	(2.539)	(0.121)
Cash flow from financing activities	0.357	26.640
Cash and cash equivalents at start of the period	94.865	59.200
Net change in cash and cash equivalents	(36.403)	(8.432)
Cash and cash equivalents at end of the period	59.200	48.099

Balance Sheet

EUR mln	2016A (Dec 31)	2017A (Sep 30)
Current Assets	62.015	50.559
Cash and Cash Equivalents	59.200	48.099
Total Assets	65.543	53.103
Equity	53.136	39.325
Current Liabilities	6.710	8.494
Borrowings	5.697	5.284

Management Capabilities

ProQR Therapeutics is being built by seasoned biotechnology innovators. The company is led by an experienced Board and management team, which has been responsible for the development of the business and has a long-term track record of developing, protecting and commercializing innovative scientific products and processes. In the past several years, the company has been investing in developing a team of experts that have a focus on patient outcomes and can deliver results. Its board and senior management team are highly experienced in the early and late stage development and commercialization of therapeutics for genetic disorders

Management Team

Daniel de Boer, Chief Executive Officer

Daniel de Boer is the company's founding Chief Executive Officer since itsincorporation in 2012. Daniel is a passionate and driven entrepreneur and advocate for CF patients, and has assembled an experienced team of successful biotech executives as co-founders and early investors. As a serial entrepreneur in IT, he founded and led a number of tech companies through phases of growth, initiating development and launch of several IT related products in several European countries. Prior to founding ProQR, Daniel served as a founder and Chief Executive Officer of RNA Systems, founder and Chief Executive Officer of PC Basic, and founder and Chief Executive Officer of Running IT. Daniel is responsible for the overall strategy and general business in the company.

Rene Beukema, Chief Corporate Development Officer

René joined ProQR in September 2013 and is a seasoned in-house corporate lawyer in the Dutch biotechnology arena. Prior to joining the company, René 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. René was also a venture partner of Aescap Venture, a life sciences venture capital firm. René is co-founder and advisor of Mytomorrows N.V., a Dutch life sciences company, and a member of the VU Medical Cancer Center children in Amsterdam. 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.

Gerard Platenburg, Chief Innovation Officer

Gerard Platenburg has served as ProQR's Chief Innovation Officer since February 2014. Gerard is a co-founder of the company and also served as the sole member of the supervisory board between August 2012 and December 2013. Gerard has an extensive background in RNA modulation and orphan drug discovery and development and is in charge of our innovation unit. Gerard has more than twenty years of senior managerial experience, which he gained during his different operational and leadership roles in growing biotech companies. Prior to joining the company, Gerard worked at Isa Pharmaceuticals B.V. from June 2009 to January 2014. Gerard co-founded Prosensa Holding N.V., growing it to become a well-known RNA modulation clinical stage company, and held various positions between April 2002 and May 2009, including Chief Executive Officer and Chief Development Officer. Gerard also worked at Pharming B.V. from April 1990 to March 2002. He is a passionate and driven pioneer of early stage technologies. Gerard has a master's degree in chemistry and molecular biology from Leiden University in 1987 and pursued PhD work at Leiden University.

Smital Shah, Chief Financial Officer

Smital Shah has served as ProQR's Chief Financial Officer since October 2014. Smital has a 12-year

track record of management and leadership in biopharma companies and investment banking, with particular experience in financial strategy and capital markets. Prior to joining ProQR, Smital was at Gilead Sciences, where she managed their multi-billion dollar debt, cash and investment portfolios. Prior to Gilead, Smital spent several years in investment banking at Leerink Partners and JP Morgan focused on capital raising and strategic transactions in the biotech space. During this time, Smital has helped raise over USD 1 billion in equity capital and over USD 7 billion in debt capital for emerging and established biotech companies as well advised on a variety of strategic transactions such as mergers, divestitures, asset sales, dividends, and royalty monetizations. Previously, she held various R&D focused roles at Johnson & Johnson. Smital has a Bachelors and Masters in Chemical Engineering and an MBA from the University of California at Berkeley.

David Rodman, Chief Development Strategy Officer

David joined ProQR in 2017 having previously served in leadership roles with Novartis Institutes for Biomedical Research (NIBR), Vertex Pharmaceuticals, miRagen Therapeutics and Nivalis Therapeutics. Prior to moving to industry in 2005, David had a distinguished academic career, leading the Center for Genetic Lung Diseases at the University of Colorado and directing the Cystic Fibrosis Care, Teaching and Research efforts at the National Jewish Medical and Research Center in Denver, Colorado. During 12 years in industry, David has had global responsibility for driving innovation in the translation of cutting-edge science into transformational new therapies for rare diseases including CF, pulmonary fibrosis, pulmonary artery hypertension and severe immunologic and inflammatory diseases. At Vertex Pharmaceuticals he directed early- and late-stage CF clinical development programs including Kalydeco®, Orkambi® and VX-661. David received a BA in Economics from Haverford College in 1976, an MD from the University of Pennsylvania in 1980 and completed training in Internal Medicine, Pulmonary and Critical Care Medicine at the University of Colorado. He has served as an advisor to the National Institutes of Health, was elected to the American Society for Clinical Investigation and is a Fellow of the American Heart Association.

Valuation

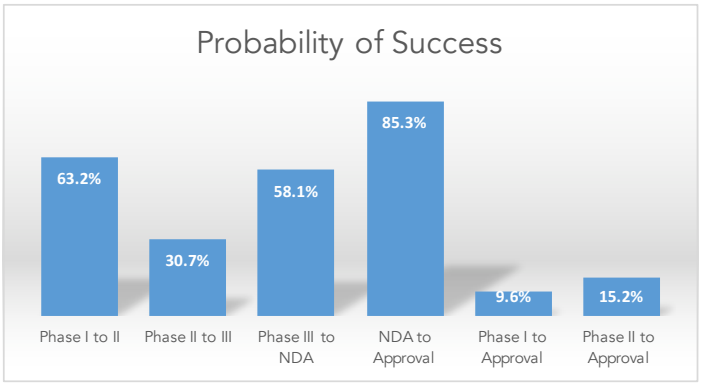
Our valuation model on ProQR Therapeutics indicates a current value of USD 350-400 million or USD 11.00-12.50 per share. At this moment we do not address value to other programs in ProQR's pipeline. This is a potential upside for the company.

Phase Success and Likelihood of Approval (LOA)

In estimating a value for each separate clinical program and products (Travelan and Protectyn) in Immuron's pipeline, we made use of several studies that were done on the clinical development success rates for investigational drugs to measure success rates for investigational drugs. We analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development. These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications. Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis.

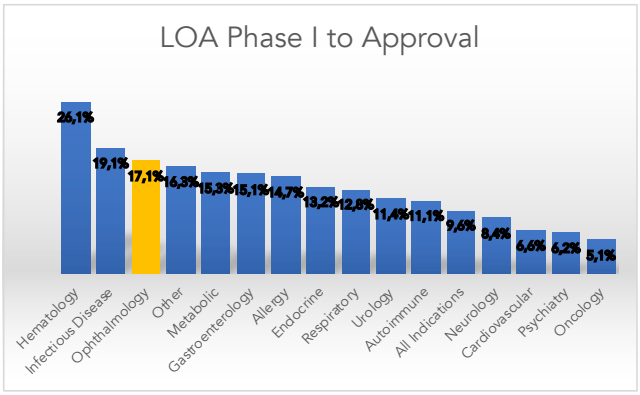
The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage where

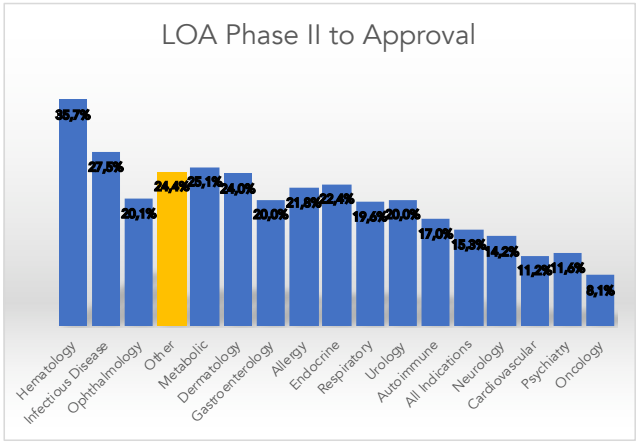
proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct. The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (see graph below)



Source: BIO Industry Analysis

Major disease areas were segmented according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. As can be seen in the graphs below, there is a wide range of Likelihood of Approval (LOA) from Phase I, II and III.





Valuation eluforsen in CF

In estimating a value for eluforsen in CF, we took into account potential markets in the USand Europe with a total number of patients of 25,000 in the US and 40,000 in Europe with a market launch in the US and Europe in 2021. We calculate a Risk adjusted Discount Rate of 15%. Annual pricing per treatment is set at USD 200,000 which is actually lower than current therapies in CF. In Europe we calculate a somewhat lower price of USD 150,000. Although we believe that ProQR will partner its program in CF with a large pharmaceutical, in our model we have calculated its value by marketing the drug independently. We estimate that a peak market share of 10-15% is possible.

In line with the report of BioMedTracker, we used a LOA of 25%. This leads to a total valuation of USD 350-400 million or USD 11.00-12.50 per share.

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	
No of patients treated US	25.1k	25.5k	25.9k	26.2k	26.6k	27.0k	27.4k	27.9k	28.3k	28.7k	
Penetration	0.50%	1.0%	2.5%	5.0%	8.0%	10.0%	12.0%	13.0%	14.0%	15.0%	
No of patients treated EU	40.0k	40.6k	41.2k	41.8k	42.4k	43.1k	43.7k	44.4k	45.1k	45.7k	
Penetration	0.50%	1.0%	2.5%	5.0%	8.0%	10.0%	12.0%	13.0%	14.0%	15.0%	
Total Revenues ($m)	57	115	291	591	959	1,217	1,482	1,629	1,781	1, 937	
Margin 40%	22.6	45.9	116.3	236.2	383.6	486.6	592.7	651.8	712.4	774.8	
WACC 15%	0.66	0.57	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19	
NPV (million)	14.9	26.2	57.8	102.1	144.2	159.1	168.5	161.1	153.1	144.8	
Total NPV (million)											**1,309**
Value per share with LOA of 25% (USD)											**10.26**

QR-110 in LCA 10

In estimating a value for QR-110 in LCA, we took into account potential markets in the US and Europe with a total number of patients of 600 in the US and 700 in Europe, in with a market launch in the US and Europe in 2020. We calculate a Risk adjusted Discount Rate of 15%. Annual pricing per treatment is set at USD 200,000 for this rare disease. In Europe we calculate a somewhat lower price of USD 150,000. Although we believe that ProQR will partner its program in CF with a large pharmaceutical, in our model we have calculated its value by marketing the drug independently. We estimate that a peak market share of 10-15% is possible. Somewhat higher compared with the report of BioMedTracker, we used a LOA of 20%.

Year	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	
No of patients treated US	644	654	663	673	683	694	704	715	725	736	
Penetration	1.0%	3.0%	6.0%	10%	18.0%	25.0%	35.0%	40.0%	45.0%	50.0%	
No of patients treated EU	721	732	743	754	765	777	789	800	812	825	
Penetration	1.0%	3.0%	6.0%	10%	18.0%	25.0%	35.0%	40.0%	45.0%	50.0%	
Total Revenues ($m)	2.7	8.3	16.9	28.5	52.2	73.5	104.5	121.2	138.4	156.1	
Margin 50%	1.4	4.2	8.5	14.3	26.1	36.8	52.3	60.6	69.2	78.1	
WACC 15%	0.76	0.66	0.57	0.50	0.43	0.38	0.33	0.28	0.25	0.21	
NPV (million)	1.0	2.7	4.8	7.1	11.3	13.8	17.1	17.2	16.8	14.8	
Total NPV (million)											**160.4**
Value per share with LOA of 20% (USD)											**1.42**

Near Term Milestones

During 2018-2019 we expect a number of important mile stones that can drive the stock price upwards. These are:

➢ QR-110 in LCA10: 6 months safety and efficacy data	2018H1
➢ Eluforsen in Cystic Fibrosis F508 del: Phase II interim data	2018H2
➢ Eluforsen in Cystic Fibrosis F508 del: Potential partnering	2018
➢ QR-313 in Dystrophic EB Exon 73: Phase I/II trial	2018H1
➢ QR-421 in Usher Syndrome Exon 13: Start clinical trial	2018YE
➢ QR-421 for Usher Syndrome Exon 13: safety and efficacy data	2019H1
➢ Axiomer RNA editing platform technology: licensing	2018/19

Competitive Landscape

ProQR's potential competitors include large pharmaceutical, biotechnology, specialty pharmaceutical, and generic drug companies, academic institutions, government agencies and research institutions. Its competitors are working on similar technologies in the field of RNA modulation 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, AGTC, Sanofi, Oxford Biomedica), gene editing (Editas Medicine; ciberer), and other approaches, including retinal implants, cell therapies, optogenetics and prevention of photoreceptor degeneration.

In the field of cystic fibrosis, a number of companies are seeking to identify and develop drug candidates for the treatment of CF, including Vertex, Galapagos/AbbVie, Proteostasis, Corbus, Spyryx Biosciences, Flatley Discovery Labs and various other companies. Of these, Vertex's Kalydeco and Orkambi are the only drugs approved to treat an underlying cause of CF, rather than the symptoms. Vertex's success in developing and commercializing Kalydeco and Orkambi could increase the resources that ProQR's competitors allocate to the development of these potential treatments for CF.

Proteostasis Therapeutics (PTI)

Proteostasis Therapeutics, Inc. is a clinical stage biopharmaceutical company developing small molecule therapeutics to treat cystic fibrosis (CF) and other diseases caused by dysfunctional protein processing. Headquartered in Cambridge, MA, the Proteostasis Therapeutics team focuses on identifying therapies that restore protein function. In addition to its multiple programs in cystic fibrosis, Proteostasis Therapeutics has formed a collaboration with Astellas Pharma, Inc. to research

and identify therapies targeting the Unfolded Protein Response (UPR) pathway. December 2017 the company reported that it has completed its Phase 2 study designed to evaluate the efficacy, safety, and tolerability of 50 mg once-a-day of PTI-428 over a 28-day treatment of CF patients on background Orkambi® (lumacaftor/ivacaftor). The addition of PTI-428 to Orkambi® demonstrated mean absolute improvements in ppFEV1 of 5.2 percentage points from baseline compared to placebo ($p < 0.05$), with mean relative improvements of 9.2 percent ($p<0.05$). This treatment effect was achieved by day 14 and sustained through 28 days of dosing. In December, Proteostasis also published data from the first five subjects (four PTI-801 treated and one placebo) of the first dose level tested in the 14-day dosing study of PTI-801 in CF patients on background Orkambi® therapy. All four subjects who received once-a-day 100 mg of PTI-801 have completed two weeks of dosing. The pharmacokinetic (PK) profile observed from these four subjects is consistent with the PK profile observed for healthy volunteers. These initial data also showed no clinically meaningful drug-drug interactions with either lumacaftor or ivacaftor. There were no serious adverse safety events reported that were considered as possibly drug related. Mean absolute improvements in ppFEV1 of approximately 4 percentage points from baseline, with mean relative improvements of approximately 7 percent, were observed in the four PTI-801 subjects who have completed two weeks of dosing to date. The first cohort of up to 20 patients is still recruiting with enrollment expected to complete in 2018Q1. The company expects to report additional data from this study in 2018Q1 as well.

Vertex (PTCT)

Vertex is focused on developing and commercializing therapies for the treatment of cystic fibrosis (CF) and advancing its research and development programs in other indications. The Company's marketed medicines are ORKAMBI and KALYDECO. ORKAMBI (lumacaftor in combination with ivacaftor) is approved as a treatment for patients having two copies (homozygous) of the Delta-F508 (F508del) mutation in their cystic fibrosis transmembrane conductance regulator (CFTR) gene.

KALYDECO (ivacaftor) is approved for the treatment of CF patients having the G551D mutation or other specified mutations in their CFTR gene. The Company's development programs in the field of CF include Tezacaftor (VX-661), VX-152, VX-440, VX-659, VX-445 and VX-371. In 2017 Total CF product revenues increased 29% to USD 2.17 billion from USD 1.68 billion for 2016. n January 10, 2018, Vertex announced that the EMA has granted extension of the Marketing Authorization for ORKAMBI in people with CF who have two copies of the *F508del* mutation to include children ages 6 through 11. In Europe, there are approximately 3,400 children ages 6 through 11 with two copies of this mutation. In the first quarter of 2018, Vertex plans to submit a New Drug Application (NDA) to the U.S. FDA and Marketing Authorization Application (MAA) line extension to the EMA for the use of ORKAMBI in children ages 2 to 5 with CF who have two copies of the *F508del* mutation. On December 7, 2017, Vertex announced positive results from an open-label Phase 3 study evaluating the safety and tolerability of KALYDECO in infants ages 1 to 2 years who have one of 10 mutations for which KALYDECO is currently approved. The study met its primary endpoint of safety, showing that KALYDECO was generally well tolerated, and safety data were consistent with those seen in previous Phase 3 studies of KALYDECO in children ages 2 to 5 years and 6 to 11 years. There was also substantial improvement in sweat chloride, a secondary endpoint, as well as in multiple measures of pancreatic function. Based on results from this study, Vertex expects to submit regulatory applications to the FDA and EMA in 2018Q1. An NDA for the tezacaftor/ivacaftor combination treatment for people with CF ages 12 and older who have two copies of the *F508del* mutation or who have at least one residual function mutation that is responsive to tezacaftor/ivacaftor is currently under priority review by the FDA with an action date of February 28, 2018. The EMA has validated the MAA for the tezacaftor/ivacaftor combination and the company expects approval in the EU in the second half of 2018. Seperately, Vertex announced the selection of two next-generation correctors, VX-659 and VX-445, to advance into Phase 3 development as part of two different triple combination regimens for people with CF. Upon the completion of regulatory discussions, the company plans to initiate a Phase 3 program in the 2018H1 to evaluate VX-659 in triple combination with tezacaftor and ivacaftor. In addition, Vertex

plans to initiate a Phase 3 program in mid-2018 to evaluate VX-445 in triple combination with tezacaftor and VX-561 as a once-daily regimen, pending additional data in 2018H1, including Phase 2 data on the combination of VX-445, tezacaftor and VX-561.

Galapagos (GLPG.BR, GLPG)

Galapagos is a clinical-stage biotechnology company specialized in the discovery and development of small molecule medicines with novel modes of action. Its pipeline comprises Phase 3, 2, 1, pre-clinical studies and discovery small-molecule and antibody programs in cystic fibrosis, inflammation, and other indications. Galapagos and AbbVie entered into a global alliance to discover, develop and commercialize novel therapies in cystic fibrosis (CF) in September 2013. Galapagos and AbbVie aim to develop a triple CFTR combination therapy to address 90% of patients with CF. In order to bring a more effective therapy to patients, the companies have developed multiple candidates and backups for each of the three components of a potential triple combination. Triple combinations of CF compounds in the portfolio have consistently shown restoration of healthy activity levels in *in vitro* assays with human bronchial epithelial (HBE) cells of patients with the F508del mutation. These combinations result in a statistically significant increase in chloride transport over Orkambi in HBE cells with the homozygous F508del mutation. In 2017, the company started three new clinical studies, concluded the FLAMINGO study in CF patients, and expects to report patient data with a first proprietary investigational triple combination therapy in mid-2018. The FLAMINGO study included 59 cystic fibrosis (CF) patients with two copies of the Class II F508del mutation and who had not received prior treatment with Orkambi or tezacaftor-ivacaftor® for four weeks prior to dosing of GLPG2222. The FLAMINGO study was over-recruited within five months. This is the first Galapagos CF patient study conducted in the United States as well as in Europe. Primary objectives of this randomized, double-blinded, placebo controlled study were to evaluate the safety and tolerability of novel C1 corrector GLPG2222. Once daily doses of GLPG2222 or placebo were administered for a total of four weeks on treatment. All patients

completed the full treatment course. Overall, GLPG2222 was well tolerated, with observed treatment emergent adverse events being predominantly mild or moderate and typical for a CF patient population. A total of four Serious Adverse Events (SAEs) were reported in three patients. Of these, two patients were on placebo, each experiencing pulmonary exacerbations due to infection. One patient was on Dose B of GLPG2222 and experienced two pulmonary exacerbations, both with onset during the follow up period; this patient had a significant sweat chloride decrease up to Day 29. There were no discontinuations due to adverse events.mFirst dosing of a CF patient has taken place in the PELICAN study, which is being run in 10 sites in Germany. The aim of the double-blind, placebo-controlled Phase 2 study is to evaluate the safety and tolerability of novel C2 corrector GLPG2737 in adult CF patients who are homozygous for the Class II F508del mutation. Patients will remain on their stable dose of Orkambi and will receive treatment with GLPG2737 over a period of 4 weeks, with up to 3 weeks' follow up. Secondary endpoints include measurements of sweat chloride, ppFEV%, and CFQ-R. Topline results are expected in H1 2018.

Spark Therapeutics (NASDAQ: ONCE)

Spark Therapeutics is a gene therapy company. The Company focuses on treating orphan diseases. It has a pipeline of product candidates targeting multiple rare blinding conditions, hematologic disorders and neurodegenerative diseases. Its pipeline includes a product candidate targeting choroideremia (CHM), which is in a Phase I/II clinical trial and a product candidate for hemophilia A, which is in a Phase I/II clinical trial. The Company's gene therapy, voretigene neparvovec (Luxturna), is intended to treat a genetic blinding condition or inherited retinal disease (IRD) caused by non sex-linked, or autosomal recessive, biallelic mutations in the RPE65 gene. Luxterna is under Priority Review with the U.S. Food and Drug Administration (FDA), with an assigned Prescription Drug User Fee Act (PDUFA) date of January 12, 2018. In October 2017, FDA's Cellular, Tissue and Gene Therapies Advisory Committee unanimously recommended (16-0) approval of Luxturna. The advisory committee's recommendation is non-binding, but FDA generally considers such

recommendations when reviewing a Biologics License Application (BLA). Luxturna has received orphan drug, breakthrough therapy and rare pediatric disease designations from FDA.

In August 2017, Spark Therapeutics' Marketing Authorization Application (MAA) for Luxturna was validated by European Medicines Agency (EMA). Luxturna also has received orphan product designations from EMA. The safety and efficacy of Luxturna were assessed in two open-label Phase 1 trials, which continue to follow participants who received Luxturna between 2007 and 2012, and one open-label, randomized, controlled Phase III trial. The Luxturna clinical program overall includes up to four years of efficacy data from a single dose. The overall safety profile has not changed over the period of observation, and has been previously reported (*The Lancet* 2016; *The Lancet* 2017).

Following the one-year control period of the Phase III study, all control participants elected to cross over and received Luxturna; long-term safety and efficacy continue to be assessed in the Phase III participants who received Luxturna between 2013 and 2015. The clinical trial program included 41 participants with vision loss ranging from mild to advanced, and included individuals from age four to 44 years at the time of first administration. Confirmed biallelic *RPE65* mutations and the presence of sufficient viable retinal cells were established in all participants.

Luxturna Phase III clinical trial data, including data from the intent-to-treat population of all randomized participants through the one-year time point, were published in *The Lancet*. Results included in the BLA submission showed a statistically significant and clinically meaningful difference between intervention (n=21) and control participants (n=10) at one year, per the clinical trial's primary endpoint, mean bilateral multi-luminance mobility testing (MLMT) score change (difference of 1.6; 95% CI, 0.72, 2.41; p=0.001). In addition, participants who received Luxturna showed a marked difference compared to control participants across the first two secondary endpoints: full-field light sensitivity threshold (FST) testing averaged over both eyes (p=0.001) and the mobility test score change for the first injected eye (p=0.001). A third secondary endpoint, the change in

visual acuity (VA) averaged over both eyes, was not statistically significant between intervention and control participants (p=0.17).

On average, participants in the original Phase III intervention group maintained functional gains observed by the day-30 visit through their last annual follow-up visit, as measured by MLMT and FST, with observation ongoing. Average improvement in FST testing observed in the original intervention group at one year was more than 100-fold (or greater than two log units).

In continuation of the trial to include crossover of the control group to receive Luxturna, 93 percent (27 of 29) of all treated Phase III trial participants saw a gain of functional vision as assessed by bilateral MLMT over the follow-up period of at least one year from administration of Luxturna to each eye. Additionally, 72 percent (21 of 29) of all Phase III trial participants receiving Luxturna successfully completed MLMT at the lowest light level evaluated (1 lux) at one year.

Horama SA (France)

Horama is a clinical-stage biotech company that develops gene-therapy treatments, based on recombinant adeno-associated virus (rAAV) vectors, targeting rare inherited retinal diseases. Horama was founded in 2014 by a complementary team of world-renown academic researchers who conducted, in 2011, one of the first clinical trials of gene therapy applied to ophthalmology in France. In July, the FDA granted Orphan Drug Designation for its program RLBP1. RLBP1 has been developed for the treatment of retinal dystrophy caused by mutations in the *RLBP1* gene HORA-RLBP1 is delivered in the form of a sterile vector suspension injected directly into the subretinal space, where it allows rapid and robust transgene expression in the targeted retinal cells.

HORA-RLBP1 is designed as a gene replacement product, i.e., to provide the cells with a non-mutated copy of the human *RLBP1* gene, thereby enabling expression of functional CRALBP and improving visual function, or at the very least significantly slowing retinal degeneration, in patients with *RLBP1* mutations.

Analyst: Marcel Wijma MSc
Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.