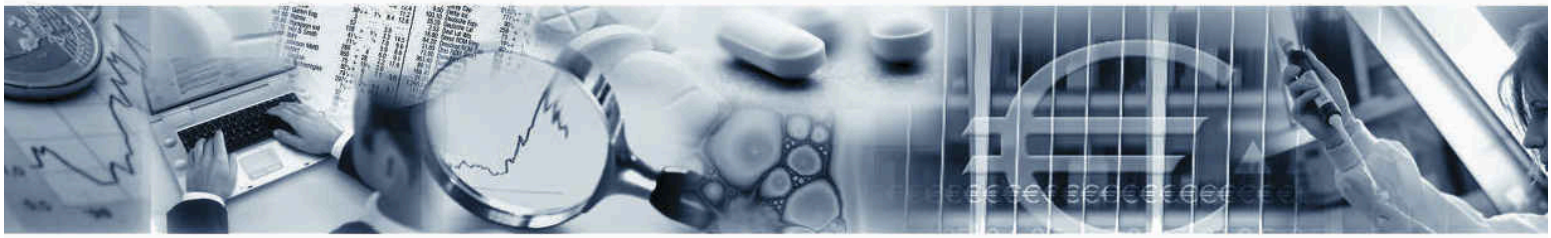


Research Note

ProQR Therapeutics

Focus on High Unmet Medical Need

Chief Research Analyst

Marcel Wijma MSc

+1 (917) 460 6185 (US)

+31 (6) 8489 2954 (NL)

m.wijma@leeuwenhoeck.com

http://www.leeuwenhoeck.com

Date: 9 May 2017

Name:	**ProQR Therapeutics**
Country:	**The Netherlands**
Price:	**USD 4.85**
ISIN Code:	**NL0010872495**
Reuters Code:	**PRQR**
Market Cap (USD m):	**113.2**
EV (USD m):	**54.0**
Cash & cash eq. (EUR m):	**59.2**
Shares outstanding (m):	**23.3**
Volume:	**64,606**
Free float:	**82%**
52-week Range:	**3.55-8.70**

EUR million	2015A	2016A	2017E
Total Revenues	3.235	1.828	2.000
Net (Loss)/Profit	(20.831)	(39.119)	(35.000)
Net (loss)/profit ps (cents)	(0.89)	(1.68)	(1.50)
R&D costs	23.401	31.923	35.000
Cash increase/(decrease)	(23.936)	(36.403)	(32.000)
Cash and marketable sec.	94.865	59.200	27.200

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 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). Although there are more than 1,900 different genetic mutations that cause CF, the Delta F508 mutation that ProQR is targeting is the most prevalent and is present in approximately 70% of all CF patients in the Western world and approximately 65,000 patients worldwide. According to data collected in June 2016 by Datamonitor Healthcare, pulmonologists surveyed indicated that more effective CFTR modulators for patients with Delta F508 mutations is the greatest unmet need in cystic fibrosis. In July 2016, QR-010 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. QR-010 is scheduled to complete a phase Ib trial, and is expected to advance into a phase II study in 2018. At the time of ECFS (June 7-10 2017) the company will provide a next update on enrollment in the study. The study is expected to have topline data in mid-2017.

- CF is a genetic disease that causes early morbidity and mortality. CF currently has no cure. The median age of death for CF patients is 30 years or less, and more than 90% of

CF patients die from respiratory failure. To date, all but two of the therapies approved to treat CF patients are designed to treat the symptoms of CF rather than address the underlying cause. CF is caused by mutations in the gene that encodes for a protein called cystic fibrosis transmembrane conductance regulator, or CFTR. It leaves without saying that the potential market for CF is worth several billions.

- The Company's current cash position is EUR 59.2 million which should be sufficient to carry out the further development of its pipeline till mid 2018. Net cash used in operating activities during the full year ended December 31, 2016 was EUR 34.2 million respectively, compared to EUR 24.2 million for the same period last year.

- **Based on NPV based valuation, we believe that ProQR is substantially undervalued at the current share price of USD 5.20. Using our valuation model and taking into account the future revenues from QR-010 and QR-110, the company's current total value should be USD 250-300 million, or USD 10.50-12.50 per share. This represents a substantial upside from the current share price.**

Company Profile & Technology Platform

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. 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, QR-010 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 QR-010 for the treatment of CF. Its lead product candidate, QR-010, 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 is currently conducted. 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 moving 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.

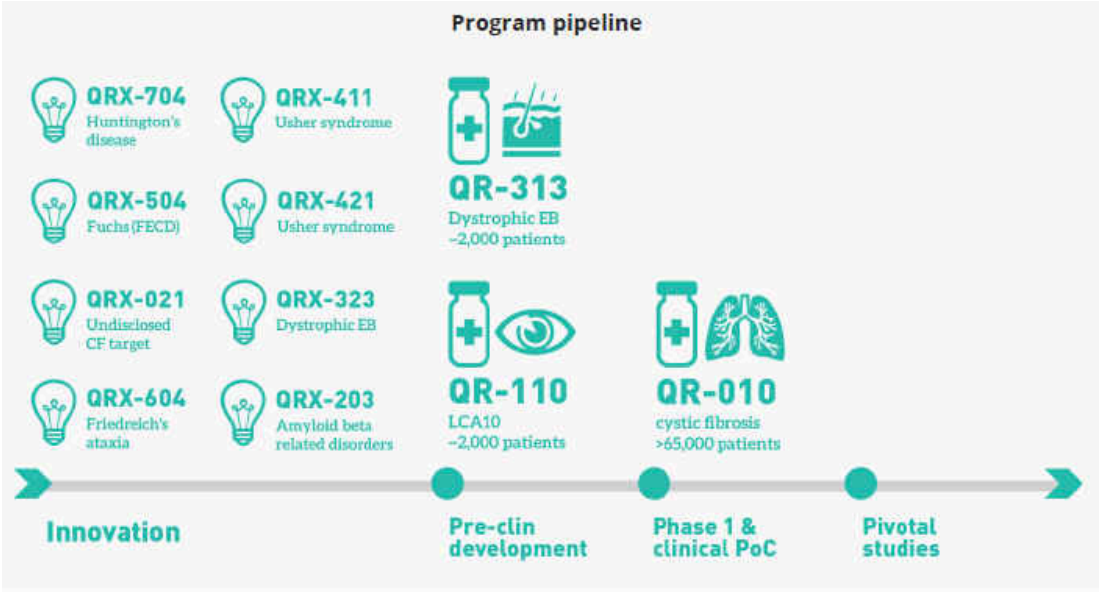
- Independently commercialize QR-010 and any other CF products that it successfully develop. ProQR intends to commercialize QR-010 itself and retain all commercial rights in major markets. There are extensive CF patient registries, and CF patients are treated in centralized, specialized care centers. Because of this well-organized CF community, the company should be able to market effectively QR-010, if approved, with an initially small,

targeted sales force in the United States and Europe.

- 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.

Pipeline: Focus on Rare Genetic Disorders

ProQR's innovation unit is its internal discovery engine, which is used to discover additional molecules through internal research and external collaborators. These pipeline programs are based on our multiple RNA technologies that were discovered internally or in-licensed. The company applies an evaluation process in identifying programs that are ready to leave the innovation unit and move into development. The criteria include established genetic causality, ability to deliver to the target organ, intellectual property protection, strong pre-clinical proof of concept, and a high unmet need. The early stage programs are in various stages of discovery and target different severe genetic disorders that include programs for Usher syndrome and Fuchs endothelial corneal dystrophy (FECD) both areas of ophthalmology with high unmet medical need. ProQR further has programs in our central nervous system, or CNS, franchise for Huntington's disease and amyloid beta related disorders. In its neuromuscular franchise the company has a program for Friedreich's ataxia.



QR-010 in CF

ProQR conducted two clinical trials of QR-010 in parallel. Study PQ-010-002 is a proof-of-concept trial evaluating the effect of topical administration of QR-010 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 QR-010 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. QR-010 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 is currently enrolling. The Phase Ib study is designed to enroll a total of 64 adult Delta F508del patients that have a relatively good lung function (ppFEV1 >70%). Patients receive either a single dose of QR-010 through inhalation, or 12 doses over the course of 4 weeks. 4 different dose groups are studied in this placebo controlled trial. Although exploratory efficacy outcomes are measured, the Phase 1b study is designed to evaluate safety and tolerability and identify an appropriate dose for subsequent Phase II and III studies, it is not powered to demonstrate efficacy in a statistical significant manner.

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 QR-010 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. The company anticipates to begin recruitment for this trial in 2018.

To achieve broad distribution to CF-affected organs, QR-010 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

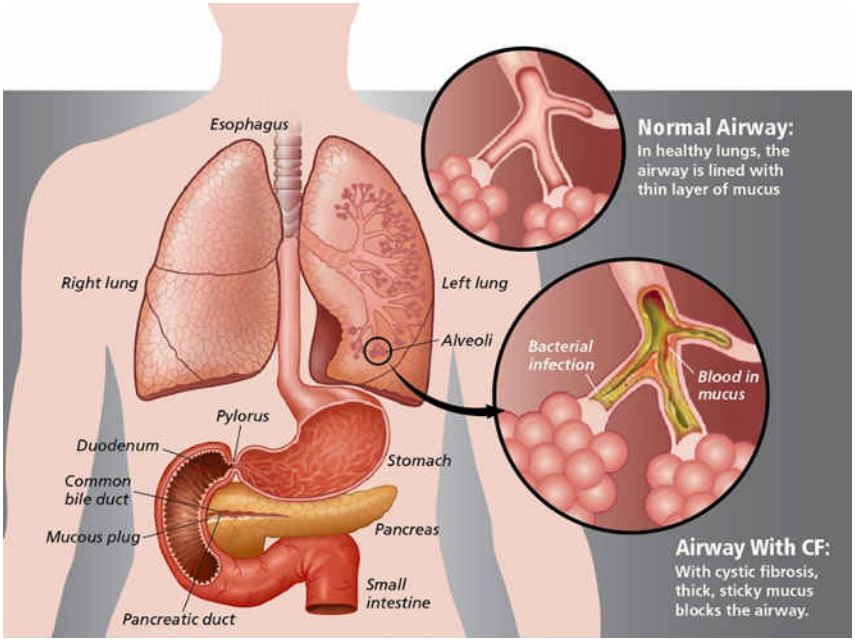
Leber's Congenital Amaurosis (LCA) is the most common genetic cause of blindness in childhood. ProQR believes that the p.Cys998X mutation in the CEP290 (Centrosomal protein of 290 kDa) gene is the most prevalent mutation which generally accounts for the most severe disease phenotype (LCA 10). Patients 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). There are currently no disease modifying treatments approved or potential treatments in clinical trials for patients with p.Cys998X associated

LCA 10, a form of LCA. 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, the company announced that the investigational new drug (IND) application was cleared to initiate 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. Top line results are expected before the end of 2018

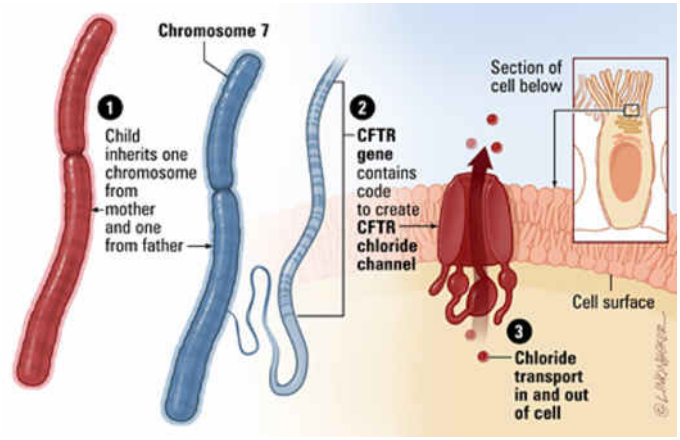
Cystic Fibrosis: Lethal Genetic Disorder

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.

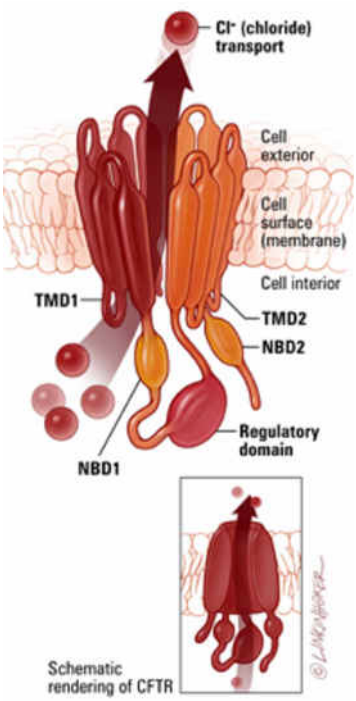


Scientific Background Cystic Fibrosis and CFTR protein

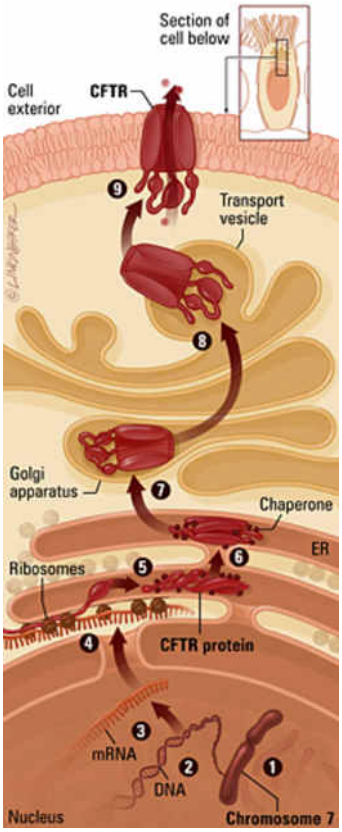
Construction and placement of the CFTR protein in the cell membrane occurs in distinct phases. Located on the long (q) arm of chromosome 7 at position 31.2, the *CFTR* gene is comprised of 27 exons that encode its genetic sequence. An exon is a portion of a DNA that contains the code for a protein structure.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



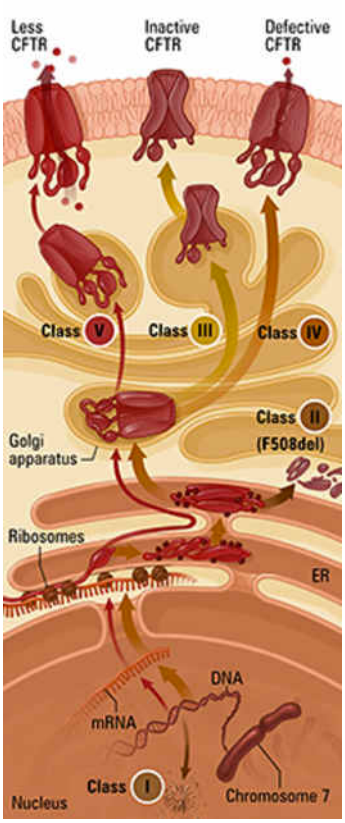
Cystic fibrosis is caused by mutations in the CFTR gene



CFTR Channel



Coding, construction and placement of the CFTR protein

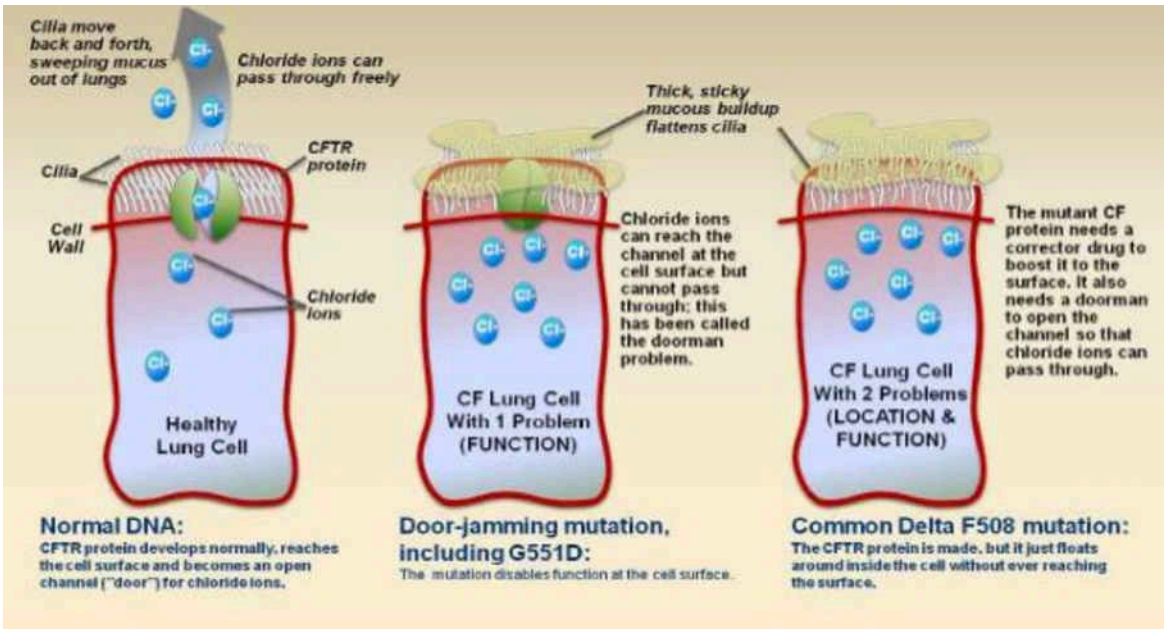


CFTR Channel mutations

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.

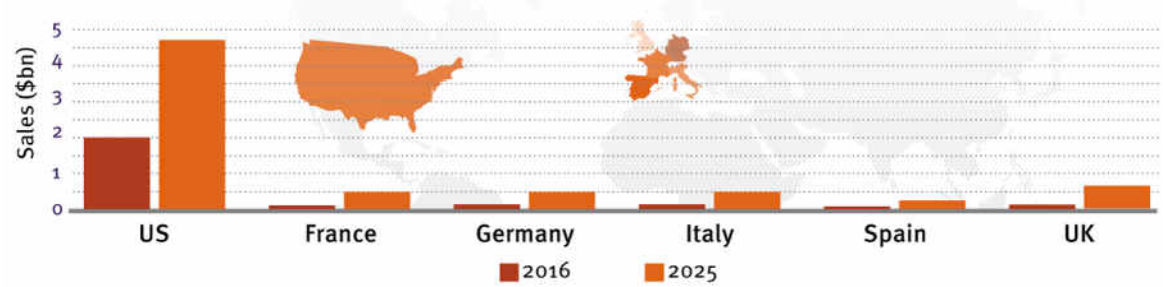


Source: J Cyst Fibros. 2012 May 11 (3): 237-45

Booming Market for CF

The CF market has changed significantly since the approval of Vertex's Kalydeco in 2013, a breakthrough product that improves treatment outcomes for certain patient populations. Now, in 2017 Vertex continues to rule the CF landscape. According to analyst models from Informa's Pharma Intelligence, recently launched Orkambi will up its US market share to 22% this year and will steadily increase its reach to 28% by 2025 – to become the most prescribed CF therapy in the

US. Orkambi, which was approved in the US in 2015, is expected to overtake by 2020 the stalwart in this market, **Roche**'s *Pulmozyme*. Other currently approved CF treatments that will steadily lose market share in the US over the next three years include Novartis' *TOBI Podhaler* and Gilead Sciences' *Cayston*. Worldwide, Orkambi is already the highest ranked CF therapy by sales, estimated to hit revenues of USD 4.9 billion in 2025.

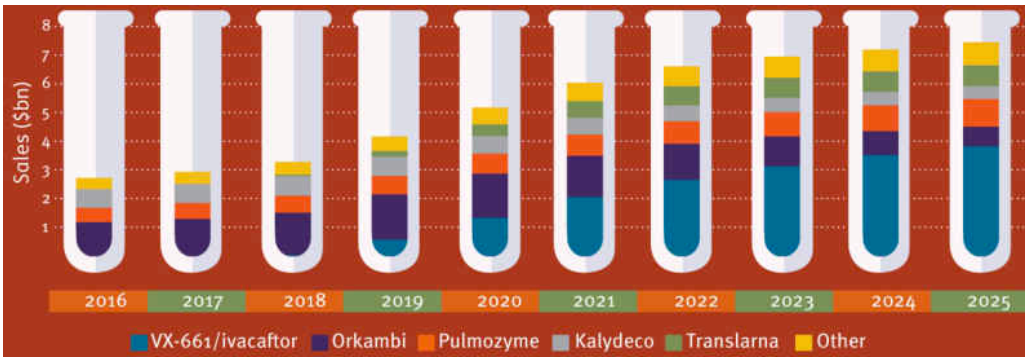


According to data collected in June 2016 by Datamonitor Healthcare, pulmonologists surveyed indicated that more effective CFTR modulators for patients with F508del mutations is the greatest unmet need in cystic fibrosis. A variety of approaches have been proposed for the treatment of Delta F508 CF, including the use of small-molecule CFTR modulators, RNA therapies, and gene therapies. Due to its monogenic nature, early clinical efforts focused on gene therapies, particularly viral gene therapies. However, success was mixed, largely due to poor transduction of lung cells and activation of immune responses against the vectors. As mentioned, the current standard of care for Delta F508 CF is Orkambi, a fixed-dose combination of the CFTR potentiator ivacaftor (Kalydeco) and the CFTR processing corrector lumacaftor. While Orkambi does improve the forced expiratory volume of Delta F508 CF patients, the effect is modest (2.6-4.0%). Moreover, treatment of Delta F508 human bronchial epithelial (HBE) cells with lumacaftor and ivacaftor only restores CFTR activity to 25% of normal. Progressive lung failure is still likely to occur, leaving lung transplantation as the only currently viable long-term therapeutic option. Taken together, current therapies for Delta F508 CF leave a substantially unmet clinical need.

Ongoing Growing interest for CF Market

The year 2016 saw CF at the center of transactions for Sanofi, AstraZeneca, Editas Medicine and Moderna Therapeutics – deals that signify the varied and growing interest in this disease space, despite Vertex's control over the market. Moderna's deal with CF expert Vertex, signed in July last year, focused on a single drug compound and could be worth more than USD 300 million to the privately held company. Moderna, in partnership with Vertex, will develop a CF therapy based on its messenger RNA (mRNA) drug development technology. Moderna is focused on getting its mRNA technology into the right cell and believes a rare genetic disease is the best route for testing its technology in the lungs. Also in 2016, gene editing company Editas signed a deal with the Cystic Fibrosis Foundation, through its affiliate the Cystic Fibrosis Foundation Therapeutics. The biotech company will get up to USD 5 million from the foundation, as well as access to its network of scientific experts in the disease, to carry out research into a CF treatment aimed at fixing the actual gene responsible for the disease. This is a different approach to currently approved therapies and most pipeline candidates. Meanwhile, in October 2016 Insmed, a global biopharmaceutical company focused on rare diseases, signed a licensing agreement with AstraZeneca for exclusive rights to AZD7986, a novel oral inhibitor of dipeptidyl peptidase I (DPP1).

Cystic Fibrosis Market Leaders



Leber's Congenital Amaurosis: Rare 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 projection 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.

Near Term Milestones

During 2017-2018 we expect a number of important mile stones that can drive the stock price upwards. These are:

- Mid-2017: Top line results QR-010 Phase Ib
- 2017: Disclosure other programs in the R&D Pipeline
- 2018: Initiating Phase II clinical trials for QR-010 in CF
- 2018: Top-line data QR-110 clinical trial in LCA 10
- 2018: Initiating and top-line data clinical trials QR-313 in DEB

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.