at a glance™

Recent Events: ***Two key clinical studies in cystic fibrosis set to report mid/late 2016; second genetic disease candidate moving towards entering the clinic during this year; full pipeline portfolio detailed at March 14th R&D Day in NYC.***

HIGHLIGHTS

- **ProQR (Nasdaq: PRQR), based in Leiden, The Netherlands and Palo Alto, CA, IPOed via Leerink Partners and Deutsche Bank late 2014, selling 8.6 million shares at $13 for net proceeds of approximately $102 million. Top three institutional holders are Fidelity, OrbiMed Advisors, and Baker Bros.**
- **Co-founders include Henri Temeer and Dinko Valerio, former CEOs of Genzyme and Crucell, respectively. Both serve on ProQR's Supervisory Board.**
- **Top-line data from two key human trials in cystic fibrosis (CF) are due mid/late 2016. They aim to validate the promising and unprecedented results of previous preclinical studies in well accepted animal models. (In genetic diseases, unlike, say, cancer or arthritis, success in well-established animal models tends to provide relatively high confidence about how the agent will work in humans.)**
- **The core technology utilizes proprietary RNA molecules to restore the functionality of genetically defective proteins.**
- **In CF, ProQR's experimental agent is designed to repair the mRNA that codes for a chloride-transporting protein responsible for keeping the lung's inner lining moist. When defective, no chloride ions can flow out of the cells, creating dehydrated sticky mucus in the lungs and other organs. Pathogens thrive in this environment and an endless cycle of infection and inflammation results in scarring and progressive life limiting destruction of the lungs. Average life expectancy is 27 years.**
- **ProQR targets the most common mutation causing CF, the ΔF508 mutation. It affects ~49,000 of the 70,000 patients worldwide. Vertex (VRTX-$23 billion market cap) was very successful because of their drugs for CF. Their first drug Kalydeco is of great therapeutic benefit but only in a small group of CF patients (G551D mutation). Their second drug Orkambi also targets the ΔF508 mutation but showed only a modest effect in clinical trials. A large unmet medical need remains in the ΔF508 population.**
- **ProQR's core technology can be leveraged beyond CF and it has launched programs for diseases in four other therapeutics categories. Target diseases include epidermolysis bullosa, Usher syndrome, Friedreich's ataxia, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease and Alzheimer's disease.**
- **ProQR plans to monetize on some of the non-core programs by partnering or out-licensing the assets, creating a source of non-dilutive funding for the company.**

ProQR Therapeutics, N.V.
(Nasdaq: PRQR)

Recent Price:	**$6.35**
Shares O/S:	**23.3 Million**
Approx. Mkt Cap:	**$148 Million**
Approx. Cash at 12/31/15:	**€95 Million**

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THE SCIENCE, BRIEFLY NOTED

ProQR's science originated at Massachusetts General Hospital, by a world renowned RNA scientist. It's a sophisticated advance in RNA technology that's designed to repair genetic defects in the messenger-RNA in a unique way, potentially leading to full restoration of normal activity of the defective proteins.

Messenger-RNA conveys the protein-making instructions issued by DNA. Defective DNA creates defective messenger-RNA, and defective messenger-RNA creates defective proteins. ProQR's technology repairs defective messenger-RNA enabling it to create active proteins.

This unique approach provides some of the perceived advantages of gene therapy without its known drawbacks, and it appears more versatile and effective than protein modulation with small molecules, an approach that dominates currently pursued therapeutic approaches to CF.

Moreover, ProQR's technology appears to be broadly applicable to a wide range of genetic disorders. In fact, the company is currently evaluating clinical programs in five therapeutic areas: respiratory, ophthalmology, central nervous system, dermatology, and neuromuscular.

QR-010 in Cystic Fibrosis

--No dose limiting toxicity in 28-day monkey study up to very high doses, far above contemplated therapeutic dose.

--Thick mucus layer is not a barrier for administration of QR-010 into the lung via inhalation. Similar distribution of the drug was seen in 'normal' mice and in mice with CF lungs.

--An unprecedented 80% restoration of normal CFTR protein function was observed in two separate 'gold standard' mouse studies – just ~25% is expect to be sufficient to address the disease.

--Data mid/late 2016: Look for top-line results of two key QR-010 studies, the Phase 1b for safety and exploratory efficacy, and the NPD study designed to illustrate the restoration of CFTR activity, the underlying cause of the disease.

About Cystic Fibrosis

CF is a progressive, life-limiting genetic disease that causes thick mucus to accumulate in vital organs like the lungs. This leads to a limited life expectancy of 27 years. There is no cure.

The culprit is a defective CFTR protein, a chloride channel that regulates the transport of fluids that coat the inner surfaces of the lungs and other organs. Patients with CF have mutated forms of CFTR protein that are less active or not active at all.

The missing or defective CFTR protein causes a buildup of sticky mucus that clogs airways and disrupts several bodily functions. Patients have difficulty breathing. Digestion is impaired. Because pathogens thrive in the mucus patients experience frequent bacterial infections and rampant inflammation. The resulting build-up of fibrotic tissue in the lung and general respiratory tract damage ultimately becomes severe, accounting for more than 95 percent of the morbidity and mortality associated with CF.

There are at least 1,800 known mutations of the disease. Not one medication is known that addresses the underlying cause of all the different mutations. QR-010 targets the most common mutation, ΔF508. It's estimated that roughly 70 percent of the 70,000 patients worldwide with CF suffer from this specific mutation.

About QR-010

QR-010 is a first-in-class RNA-based oligonucleotide designed to address the underlying cause of cystic fibrosis by repairing the mRNA defect encoded by the ΔF508 mutation in the CFTR gene of CF patients.

The ΔF508 mutation is a deletion of three of the coding base pairs, or nucleotides, in the CFTR gene, which results in the production of a misfolded CFTR protein that does not function normally.

QR-010 is designed to bind to the defective CFTR mRNA and guide the insertion of the three missing nucleotides, thus repairing the mRNA and subsequently producing normal CFTR protein. QR-010 is designed to be self-administered through a small, handheld aerosol delivery device, or nebulizer, in the form of a mist inhaled into the lungs.

The aerosol delivery is designed to allow maximum exposure of QR-010 to the primary target organ, the lung, as well as significant exposure to other affected organs through systemic absorption into the blood. QR-010 has been granted orphan drug designation in the U.S. and European Union.

QR-010 Clinical Status

A global Phase 1b clinical trial started in June 2015 is utilizing aerosolized QR-010 in 64 patients that are homozygous (carry two copies) for the ΔF508 mutation. This study is primarily assessing safety and pharmacokinetics, but it will also document exploratory measures of efficacy commonly used to see if a medicine is beneficial in CF patients.

Patient enrollment is accelerating and top-line data is due mid/late 2016.

The second trial is a nasal potential difference, or NPD, study started in September 2015. It will enroll up to 32 patients that are either homozygous (carry two copies) for the ΔF508 mutation or are compound heterozygous for the ΔF508 mutation (one copy of the ΔF508 plus one other CF disease causing mutation).

Why NPD? It's a well-accepted diagnostic test and is used to assess the therapeutic benefit of investigational agents in CF. It measures the transport of chloride through the CFTR protein channel, the lack of which is the underlying cause of CF. Animal models of CF have shown QR-010's ability to restore NPD to normal levels. This current proof-of-concept study aims to repeat the same test in humans and therefore provide important confirmation of the therapeutic potential of QR-010 in CF.

Expanding the Pipeline

ProQR has set up an in-house discovery engine that they call the innovation unit. This is a dedicated group working on applying the company's toolbox of RNA technologies to other diseases. This significant effort is led by Gerard Platenburg.

Since its inception in 2014, this specialized group has produced numerous promising programs including programs in epidermolysis bullosa, Usher syndrome, Friedreich's ataxia, Fuchs endothelial corneal dystrophy (FECD), Huntington's disease and Alzheimer's disease.

The company recognizes that not all of these programs can be developed in-house and has therefore initiated an active business development strategy to either partner, out-license or spin out some of these programs.

QR-110 for Restoring Sight

The second indication for ProQR's RNA technology may restore sight lost due to a rare childhood disease, Leber's congenital amaurosis, or LCA. It's the first program to come out of the Innovation Unit, ProQR's in- house discovery engine responsible for new drug development programs utilizing the company's core RNA technology.

LCA is the leading cause of genetic blindness in children. QR-110 targets the most common genetic mutation causing the disease, which affects about 2,000 patients in the Western world.

Preclinical work has been very promising. During 2016 the company is moving the program towards starting a Phase 1b trial directly in LCA patients.

Summary Points

- **Top-line results of two key clinical trials of QR-010 in cystic fibrosis scheduled to readout mid/late 2016. These trials could provide a confirmatory bridge to pivotal trials. QR-010 has been accorded orphan drug designation in the U.S. and Europe.**
- **QR-010 is designed to treat a genetic mutation of CFTR protein that is found in nearly 70 percent of all CF patients, creating a very significant market opportunity.**
- **During 2016 the company is moving it's second program towards clinical studies targeting the most common genetic cause for childhood blindness.**
- **ProQR is pursuing programs using its core RNA technologies in five therapeutic areas, each with pressing needs for disease-modifying medicines. These programs will be housed in separate entities and the company will capitalize on some of these assets with cash from partners or licensing deals.**
- **At December 31, 2015, ProQR held cash and cash equivalents of €95 million.**

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