This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to," "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. Such statements include those relating to our ProQR Vision 2023 strategy and our key 2019 goals, the development and therapeutic potential of our product candidates, including sepofarsen, QR-1123, QR-421a, QR-411a, QR-504, the potential of our Axiomer® editing platform, our plans and timing of initiating and obtaining results from our ongoing and planned clinical trials, our plans for building commercial infrastructure to support the launch of our product candidates, if approved, our plans and timing of submitting applications for marketing approval of our product candidates, our expectations for our platform and discovery of new product candidates, and our plans for strategic collaborations and alliances for our programs.

Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this press release. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the risks, uncertainties and other factors in our filings made with the Securities and Exchange Commission, including certain sections of our annual report filed on Form 20-F. These risks include, but are not limited to, any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, we may not realize the intended benefits of our current and potential future strategic collaborations, we may not discover or develop any new product candidates, including through our Axiomer® platform, that prior results observed from preclinical or clinical trials, will not be replicated or will not continue in ongoing or future studies or trials, that we may not successfully submit applications for marketing approval for our product candidates on time or at all, that regulatory authorities may require additional clinical trials beyond those that we currently contemplate conducting, that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and growth potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-party suppliers and manufacturers, risks regarding the accuracy of our estimates of expenses and future revenue, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future, except as required by law.
Agenda

8:00 – 8:05  Smital Shah  
*Chief Business and Financial Officer*

8:05 – 8:20  Daniel de Boer  
*Founder & Chief Executive Officer*

8:20 – 8:35  Aniz Girach, MD  
*Chief Medical Officer*

8:35 – 9:20  David Rodman, MD  
*Executive Vice President of Research & Development*

9:20 – 9:30  Q&A

9:30 – 10:00  Break

10:00 – 10:20  Thaddeus (Ted) Dryja, MD  
*Professor of Ophthalmology*

10:20 – 10:45  Peter Adamson, Ph.D.  
*Head of Ophthalmology Research*

10:45 – 11:00  Gerard Platenburg  
*Chief Innovation Officer*

11:00 – 11:10  Q&A

11:10 – noon  Lunch
ProQR’s Vision 2023

Daniel A. de Boer, Founder & Chief Executive Officer
The ProQR Journey

- **2012**: Founding of ProQR
- **2014**: IPO on Nasdaq and expansion of pipeline
- **2015**: Start of *sepofarsen* trial in LCA10
- **2016**: Start of CF clinical trials
- **2017**: Readout of CF trials
- **2018**: Positive clinical data of *sepofarsen*
- **2019**: Expanding the Ophthalmology pipeline to capture the opportunity
Eyes on the Opportunity

Foundation of common characteristics, irrespective of the target

- Intravitreal administration is routine procedure
- Acceptable safety profile
- Broad distribution throughout the entire retina
- Long half life allowing for infrequent dosing

The opportunity:

- >100 tangible targets remain after further filtering for disease state and population size

ProQR projects its technology can address about 25% of the mutations at a molecular level

- >300 genes causing Inherited Retinal Diseases, described with >50 pathogenic mutations per gene, leading to >15,000 targets.
ProQR’s VISION 2023

A FULLY INTEGRATED INHERITED RETINAL DISEASE COMPANY BY 2023

2 COMMERCIAL PRODUCTS

3 LATE STAGE PROGRAMS

7 EARLY STAGE PROGRAMS
Discovery engine
• Specialized integrated discovery engine
• Discovering 10 or more new IRD drugs per year
• Use human optic cups to pre-clinically validate clinical molecules

Development
• Utilize digital clinical trials
• Use innovative Bayesian adaptive designs to accelerate time to NDA / MAA

Commercial
• Establish IRD specialized commercial infrastructure in North America and Europe
• Focused on ~approx. 30 specialist centers that treat majority of IRD patients
• Leverage commercial infrastructure for multiple products to same call points
# ProQR key development pipeline

<table>
<thead>
<tr>
<th>Ophthalmology</th>
<th>DISCOVERY</th>
<th>PRECLINICAL DEVELOPMENT</th>
<th>PROOF OF CONCEPT TRIALS</th>
<th>LATE STAGE/REGISTRATIONAL TRIALS</th>
</tr>
</thead>
<tbody>
<tr>
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<td>QR-1123 for P23H adRP - <em>discovered by Ionis</em></td>
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<tr>
<td>QR-504 for FECD3</td>
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<tr>
<td>QR-411 for Usher syndrome 2A PE-40</td>
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<tr>
<td>QRX-136 for LCA undisclosed mutation</td>
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<tr>
<td><strong>Beyond ophthalmology</strong></td>
<td></td>
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<tr>
<td>QR-313 for DEB exon 73</td>
<td></td>
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</tr>
<tr>
<td>QRX-704 for Huntington's Disease</td>
<td></td>
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</tr>
</tbody>
</table>
5 IRD drugs in clinical trials in next 18 months

- **Sepofarsen for LCA10**
  - Start enrollment Phase 2/3

- **Sepofarsen**
  - 12 month data Phase 1/2

- **Sepofarsen**
  - Phase 2/3 fully enrolled

- **QR-411 for Usher PE-40**
  - IND submission and start trial

- **QR-1123 for adRP**
  - open IND and first patient dosed Phase 1/2

- **QR-1123**
  - Interim readout Phase 1/2

- **QR-1123**
  - Full readout Phase 1/2

- **QR-504 for FECD**
  - IND submission and start trial

- **Sepofarsen**
  - Top-line data Phase 2/3

*Discovery of 10 new development candidates per year*
Building ProQR’s commercial infrastructure

- Patients are typically seen at one of the approximately 30 IRD hub centers in North America and Europe
- A compact market that can be covered by a limited number of sales reps
- ProQR intends to market multiple IRD products in EU and North America independently, and find partners for ROW
- Pre-commercialization activities underway
  - Building KOL engagement
  - Engaging payers and exploring innovative reimbursement models
  - Launch planning for sepofarsen launch in 2021
Drugs in development for >100,000 patients

- Sepofarsen for LCA10
- QR-421a for Usher Syndrome
- QR-1123 for P23H adRP
- QR-411 for Usher Syndrome
- QR-1011 for Stargardt’s Disease
- QRX-461 for Usher Syndrome
- QRX-136 for LCA10
- QR-504 for FECD
ProQR’s Vision 2023

A Fully Integrated Inherited Retinal Disease Company by 2023

2. Commercial Products
3. Late Stage Programs
7. Early Stage Programs
Aniz Girach, MD – Chief Medical Officer

- Most recently Chief Medical Officer at Nightstar Therapeutics overseeing development of gene therapies for IRD
- Experience in academia and industry at Eli Lilly, Merck, Alcon and ThromboGenics
- Oversaw development and approval of Ocriplasmin (Jetrea) a first in class biologic therapy for retinal disease
- Honorary Professorship at Wills Eye Hospital, Philadelphia
- Member of 3 Scientific Advisory Boards for international ophthalmic organizations currently
- Reviewer for 5 peer-reviewed journals, including Eye and IOVS
- Edited 4 books and author of over 100 scientific abstracts and manuscripts
RNA therapies for IRDs

Aniz Girach, MD, Chief Medical Officer
Opportunity of RNA therapies for IRDs

- High unmet medical need
  - Rational design/ broad applicability
  - Ease of delivery, wide distribution
  - Acceptable safety profile
  - Promising efficacy
IRD management coming of age

• Improved diagnosis

• **New Treatment options**
  • Gene therapies
    • Luxturna for LCA2
    • Experimental therapies for other IRDs
      • Eg choroideremia, RP
  • RNA therapies
    • Macugen for Wet AMD
    • Vitravene for CMV Retinitis
    • Experimental therapies for other IRDs
      • Eg ASO for LCA10, Usher syndrome
How do RNA oligonucleotide drugs compare with gene therapy?

<table>
<thead>
<tr>
<th>RNA Oligonucleotide Therapy</th>
<th>Gene Therapy/Editing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific</td>
<td>Specific (replaces or edits)</td>
</tr>
<tr>
<td>Requires re-dosing</td>
<td>Potential one and done dosing</td>
</tr>
<tr>
<td>Naked, no vectors needed</td>
<td>Editing material is contained within viral vectors</td>
</tr>
<tr>
<td>Under local anesthesia</td>
<td>Usually requires general anesthesia</td>
</tr>
<tr>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Intravitreal Injection</td>
<td>Sub-retinal surgery with vitrectomy</td>
</tr>
<tr>
<td>Can be used in earlier disease, since central/peripheral retinal exposure</td>
<td>Usually suitable for end-stage disease only, since applied to sub-macular area</td>
</tr>
</tbody>
</table>
Opportunity of RNA therapies for IRDs

- High unmet medical need
  - **Rational design/ broad applicability**
- Ease of delivery, wide distribution
- Acceptable safety profile
- Promising efficacy
Rational design: efficient lead selection in ophthalmology

Selection based on:
- Splice-factor prediction
- Off-target binding
- Target RNA–oligo binding
- Thermodynamic properties

Selection based on:
- *In vitro* efficacy (including retinal organoid model)
- Low immunogenicity
- Low toxicity
- Good manufacturability

Efficient *in silico* screen

25 AONs screened on average

Lead molecule selected
Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
  - Ease of delivery, wide distribution
- Acceptable safety profile
- Promising efficacy
RNA therapy delivery and distribution

**EASE OF DELIVERY AND BROAD RETINAL DISTRIBUTION**

**Intravitreal delivery is routine procedure**

- Routine procedure allows wide patient accessibility
- Long half-life in the eye allows for dosing 2-4 times per year or less frequent
- Chemical modifications enable naked delivery

**Broad distribution allows for targeting of central and peripheral diseases**

- Oligo’s distribute broadly to all different cell types and layers, including retina and cornea
- Suitable for targeting central and peripheral disease
Comparing intravitreal delivery of RNA to subretinal delivery used in gene therapy

**RNA Therapy**
*Intravitreal administration*

Injection in side of the eye depositing the drug in the vitreous for broad delivery throughout all cell layers in the eye.

**Gene Therapy**
*Sub-retinal surgery used for delivery*

1. A light and a needle are inserted into the eye to locate the place of injection.
2. 3 ports are generated in the wall of the eye to allow access for tools.
3. Vitrectomy: The vitreous gel is cut/sucked out of the eye to aid visualization and ease of injection.
4. The needle enters the retina, lifting off the retina until a bleb is formed, then depositing drug in the subretinal space.
Complications of subretinal surgery

- Sub conjunctival hemorrhage/chemosis
- Enlargement of sclerotomies with thin sclera/prior surgery
- Losing tunnels in trocar insertion
- Suprachoroidal hemorrhage/subretinal infusion
- Accidental removal of infusion
- Vitreoretinal incarceration at sclerotomies
- Leaking entry sites
- Endophthalmitis
- Cataract development
- Lens subluxation
- Anterior chamber flattening

- Posterior capsule rupture/zonular dialysis
- PVD induction complications
- Intraoperative complications with tamponades
- Iatrogenic retinal tears
- Retinal detachment
- Raised IOP
- Intraoperative hemorrhages
- Macular folds
- Loss of vision
- Hypotony related complications
- General anesthesia complications

## Complications due to IVT/drugs

### Complications of IVT injection
- Infection
- Hemorrhage
- Wound leakage
- Lens touch/cataract
- Increased IOP

### Complications due to IVT drugs
- Inflammation/immunogenicity
- Retinal/macular edema
- Arterial thrombo-embolic events*
- Retinal degeneration
- Cataracts
- Retinal detachment

* Lucentis: Most commonly used IVT drug, has arterial thrombo-embolic event rate 10.4-10.8%; Stroke rate 2-4.8% (Source: Lucentis PI)

---

**AEs are manageable with most IVT drugs**
Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
- Ease of delivery, wide distribution
  - Acceptable safety profile
- Promising efficacy
# Sepofarsen: manageable safety profile

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Lens Opacities</th>
<th>Lens Replacement</th>
<th>CME/Retinal Edema</th>
<th>Increased IOP</th>
<th>Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iluvien</td>
<td>DME</td>
<td>82%</td>
<td>80%</td>
<td>ND</td>
<td>34%</td>
<td>2%</td>
</tr>
<tr>
<td>Ozurdex</td>
<td>DME</td>
<td>68%</td>
<td>61%</td>
<td>ND</td>
<td>28%</td>
<td>2%</td>
</tr>
<tr>
<td>Yutiq</td>
<td>Uveitis</td>
<td>56%</td>
<td>ND</td>
<td>11%</td>
<td>22%</td>
<td>3%</td>
</tr>
<tr>
<td>Macugen</td>
<td>wAMD</td>
<td>10-40%</td>
<td>ND</td>
<td>1-5%</td>
<td>10-40%</td>
<td>1-5%</td>
</tr>
<tr>
<td>Lucentis</td>
<td>wAMD/DME</td>
<td>11-28%</td>
<td>ND</td>
<td>5-11%</td>
<td>7-24%</td>
<td>1-18%</td>
</tr>
<tr>
<td>Vitravene</td>
<td>CMV Retinitis</td>
<td>5-20%</td>
<td>ND</td>
<td>5-20%</td>
<td>ND</td>
<td>7-10%</td>
</tr>
<tr>
<td>Sepofarsen*</td>
<td>LCA10</td>
<td>50%</td>
<td>16%</td>
<td>Not observed**</td>
<td>Not observed</td>
<td>Not observed</td>
</tr>
<tr>
<td>Luxturna</td>
<td>LCA2</td>
<td>20%</td>
<td>ND</td>
<td>ND</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Post Vitrectomy***</td>
<td>IRD Gene therapy</td>
<td>45%</td>
<td>37%</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Ph 1/2 80µg dose group (pivotal dose)  ** CME was seen in 160µg dose group in the Ph 1/2 trial  ***Feng et al, 2014  ND: non-disclosed in Prescribing Information

**Lens opacities and CME are manageable in routine clinical practice**
Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
- Ease of delivery, wide distribution
- Acceptable safety profile
  - Promising efficacy
Promising efficacy observed for sepofarsen

First time in severe photoreceptor disease, a meaningful concordant response seen across all end points

BCVA

FST

Mobility

OCI

Change from baseline (LogMAR)

Change from baseline (Log10 photo-cd/m²)

Change from baseline (LogMAR)

Change from baseline (Log10 photo-cd/m²)

Change from baseline (LogMAR)

Change from baseline (Log10 photo-cd/m²)
Opportunity of RNA therapies for IRDs

- High unmet medical need
- Rational design/ broad applicability
- Ease of delivery, wide distribution
- Acceptable safety profile
- Promising efficacy
Inherited Retinal Dystrophies
A major opportunity for ProQR RNA therapeutics

David Rodman, MD, Executive Vice President of Research & Development
# Ophthalmology pipeline

Building on success of sepofarsen

<table>
<thead>
<tr>
<th>DISCOVERY</th>
<th>PRECLINICAL DEVELOPMENT</th>
<th>PROOF OF CONCEPT TRIALS</th>
<th>LATE STAGE/REGISTRATIONAL TRIALS</th>
</tr>
</thead>
</table>

## Ophthalmology

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepofarsen (QR-110) for LCA10 p.Cys998X</td>
<td>DISCOVERY</td>
</tr>
<tr>
<td>QR-421a for Usher syndrome 2A exon 13</td>
<td>PRECLINICAL</td>
</tr>
<tr>
<td>QR-1123 for P23H adRP - discovered by Ionis</td>
<td>DEVELOPMENT</td>
</tr>
<tr>
<td>QR-504 for FECD3</td>
<td></td>
</tr>
<tr>
<td>QR-411 for Usher syndrome 2A PE40</td>
<td></td>
</tr>
<tr>
<td>QR-1011 for Stargardt’s disease c.5461-10T&gt;C</td>
<td></td>
</tr>
<tr>
<td>QRX-461 for Usher syndrome undisclosed mutation</td>
<td></td>
</tr>
<tr>
<td>QRX-136 for LCA undisclosed mutation</td>
<td></td>
</tr>
</tbody>
</table>

- Acceptable risk/benefit safety profile (sepofarsen)
- Durable response with infrequent dosing
- Intravitreal administration delivers to the retina
- Clinically meaningful vision improvement in a majority of low vision patients
- Optic cup accurately predicted:
  - Clinically efficacious intravitreal dose level
  - Response to treatment
  - Time to onset of response
- To be further validated in future trials of sepofarsen and other IRD programs
Efficient, predictive translational platform

Three years from target selection to start of pivotal program

YEAR 1

Discovery

Organoid

CMC

YEAR 2

YEAR 3

YEAR 4

Toxicology

FIH/Ph1/2
ProQR Ophthalmology leverages platform synergies with potential to treat ~300 diseases

- Efficient rational drug design
- Predictive human-derived ex vivo organoid screening platform
- Long tissue half-life supports an optimized dosing regimen
- Rapid clinical development leading to broad platform de-risking
Translation from retinal organoids to clinical trials

Restoration of cilium and outer segment in LCA10 and Ush2a
# Efficient, predictive translational platform

*Three years from target selection to start of pivotal program*

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° screen in transfected cells</td>
<td>2° screen in retinal organoid model</td>
<td>GLP NHP PK/(PD) and toxicology</td>
<td>FIH/Phase 1/2 12 month clinical trial</td>
</tr>
<tr>
<td>Optimize on-target molecular activity</td>
<td>Characterize naked oligo molecular activity</td>
<td>Generate predictive PK/PD and TK models</td>
<td>Execute proof-of-concept (3-6m IA) and dose selection</td>
</tr>
<tr>
<td>Trigger organoid model</td>
<td>Trigger CMC</td>
<td>Trigger IND/CTA</td>
<td>Trigger pivotal program</td>
</tr>
<tr>
<td>3-6 months</td>
<td>9-12 months</td>
<td>6-12 months</td>
<td>12-18 months</td>
</tr>
</tbody>
</table>
FIH, Phase 1/2 design philosophy

*Strong GO triggers accelerated development*

<table>
<thead>
<tr>
<th></th>
<th>Strong GO</th>
<th>GO</th>
<th>Equivocal</th>
<th>NO GO</th>
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</thead>
<tbody>
<tr>
<td>Mechanistic PoC – pharmacodynamic endpoint</td>
<td>✔️</td>
<td>✔️</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Clinical PoC - registration endpoint</td>
<td>✔️</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Development dose regimen</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Preliminary risk/benefit</td>
<td>✔️</td>
<td>+/-</td>
<td>-</td>
<td></td>
</tr>
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</table>

ProQR Therapeutics – R&D Day 2019
Initial ProQR disease indications provide broad platform de-risking

<table>
<thead>
<tr>
<th>Location</th>
<th>1° Outcome measure</th>
<th>ProQR Pipeline</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macula</td>
<td>Visual acuity</td>
<td>Sepofarsen LCA10</td>
<td>Late clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QRX-1011 Stargardt's</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Peripheral (moderate to advanced)</td>
<td>Visual fields, Visual acuity</td>
<td>QR-421a Ush2a</td>
<td>Early clinical</td>
</tr>
<tr>
<td>Peripheral (early to moderate)</td>
<td></td>
<td>QR-1123 adRP</td>
<td>IND submission</td>
</tr>
<tr>
<td>Macula (advanced)</td>
<td></td>
<td>QR-411 Ush2a</td>
<td>IND-enabling</td>
</tr>
</tbody>
</table>

Peripheral Early
Peripheral Advanced
Macula (advanced)
## Snapshot of clinical-stage ophthalmology programs

### Progressive platform validation and indication expansion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Development Stage</th>
<th>Development De-risking</th>
<th>Status</th>
<th>Next milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>sepoferesan</td>
<td>LCA10</td>
<td>Pivotal</td>
<td>✓ Photoreceptor delivery ✓ Splice correction ✓ Central retinal efficacy</td>
<td>✓ 3-month efficacy and up to 12 m safety</td>
<td>Start pivotal H1 2019 Ph1/2 trial completion H2 2019</td>
</tr>
<tr>
<td>QR-421a</td>
<td>Ush2a</td>
<td>FIH/PoC</td>
<td>• Exon skipping • Peripheral retinal efficacy</td>
<td>Site initiation and screening</td>
<td>Start Phase 1/2 mid-2019</td>
</tr>
<tr>
<td>QR-1123</td>
<td>adRP</td>
<td>IND-ready</td>
<td>• RNA knockdown • Allele-specific suppression</td>
<td>IND preparation</td>
<td>Ph 1/2 start H2 2019</td>
</tr>
</tbody>
</table>
Sepofarsen (QR-110) for LCA10

**LCA10**
- Lose sight in first years of life
- No therapy available
- p.Cys998X mutation affects ~2,000 patients in the Western world

**Sepofarsen**
- **Goal:** Restore vision/ prevent vision loss in patients with LCA10
- Locally administered in the eye. Routine intravitreal procedure
- Anticipated infrequent dosing of 2 times a year

- Established modality in eye
- Strong preclinical proof of concept in human retina in preclinical models
- Orphan drug designation
- Fast track designation
- Phase 1/2 interim analysis showed rapid and sustained efficacy and favorable safety
- Pivotal phase 2/3 trial expected to start in H1 2019
LCA10 Clinical Phenotype

Cone-sparing makes LCA10 an ideal candidate for restorative RNA therapy.
Retinal Organoid: QR-110-treated c.2991+1655A>G human LCA10 retinal organoids regrow cilium

Differentiated retinal organoids

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>10µM QR-110</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td><img src="image" alt="Untreated Image" /></td>
<td><img src="image" alt="10µM QR-110 Image" /></td>
</tr>
</tbody>
</table>

QR-110 corrects CEP290 mRNA

<table>
<thead>
<tr>
<th>Untreated</th>
<th>QR-110 (µM)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

![Gene Expression Graph](image)

Ciliated cells (%)

<table>
<thead>
<tr>
<th>Untreated</th>
<th>Control</th>
<th>0.3</th>
<th>1</th>
<th>3</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td><img src="image" alt="Normal Graph" /></td>
<td><img src="image" alt="Control Graph" /></td>
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<tr>
<td>LCA10</td>
<td><img src="image" alt="LCA10 Graph" /></td>
<td><img src="image" alt="LCA10 Graph" /></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LCA10 + QR-110</td>
<td><img src="image" alt="LCA10 + QR-110 Graph" /></td>
<td><img src="image" alt="LCA10 + QR-110 Graph" /></td>
<td></td>
<td></td>
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</table>

Mean cilia length (µm)

<table>
<thead>
<tr>
<th>Untreated</th>
<th>Control</th>
<th>0.3</th>
<th>1</th>
<th>3</th>
<th>10</th>
</tr>
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<tr>
<td>Normal</td>
<td><img src="image" alt="Normal Graph" /></td>
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<tr>
<td>LCA10</td>
<td><img src="image" alt="LCA10 Graph" /></td>
<td><img src="image" alt="LCA10 Graph" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCA10 + QR-110</td>
<td><img src="image" alt="LCA10 + QR-110 Graph" /></td>
<td><img src="image" alt="LCA10 + QR-110 Graph" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OCT imaging demonstrated regeneration of outer segment after sepolfarsen treatment

**Normal retina**

EZ line in normal retina shows outer segments by EZ-line, as detected by OCT

**LCA10 retina**

EZ line in missing in LCA10 retina due to lack of outer segments

**Restoration of EZ-line in subject**

No change detected in untreated eye (data not shown)
Ongoing Phase 1/2 trial

Open label, multiple dose, dose escalation study, Phase 1/2

- Enrolled eleven p.Cys998X LCA10 patients in range of 8-44 yo
- Intravitreal injections in one eye
- Participating sites: major sites in EU (UGhent) and US (UPenn, UIowa)
- Primary endpoints: Safety, tolerability
- Secondary endpoints and exploratory efficacy: Visual acuity, mobility course, FST, OCI, pharmacokinetics, OCT, PRO, ERG, pupilometry
- Orphan drug designation in EU and US
- FDA Fast-track designation

*Loading dose is double the maintenance dose
★ = DSMC review

- Adult 80 µg*
- Adult 160 µg
- Pediatric 80 µg*
- Pediatric 160 µg

- 3 month positive interim analysis data reported in September 2018
  - >60% of patients improved on multiple efficacy endpoints

- Patients continue to be followed out to 12 months of treatment of which data is expected in H2 2019
- Eligible patients will be rolled over into an extension trial where they will be offered to also get their second eye treated

Adult 160 µg

Pediatric 160 µg
## Top line efficacy results

Concordant improvement in all outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Direction of improvement</th>
<th>Responder threshold</th>
<th>Change from baseline at Month 3 Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥ -0.3</td>
<td>Treated</td>
</tr>
<tr>
<td>Visual Acuity (ETDRS/BRVT – LogMAR n=8)</td>
<td>↓ = improved</td>
<td></td>
<td>-0.67 (0.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥2</td>
<td>Untreated</td>
</tr>
<tr>
<td>Mobility Course – level n=7</td>
<td>↑ = improved</td>
<td></td>
<td>2.57 (1.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.36 (1.04)</td>
</tr>
<tr>
<td>Full field stimulus red (FST red) - cd/m2 n=7</td>
<td>↓ = improved</td>
<td></td>
<td>-0.74 (0.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.23 (0.18)</td>
</tr>
<tr>
<td>Full field stimulus blue (FST blue) - cd/m2 n=7</td>
<td>↓ = improved</td>
<td></td>
<td>-0.91 (0.38)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-0.02 (0.11)</td>
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<tr>
<td>Nystagmus tracking (OCI) - Log_{10} mm n=7</td>
<td>↓ = improved</td>
<td></td>
<td>-0.14 (0.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.04 (0.06)</td>
</tr>
</tbody>
</table>
Full Field Stimulus Test (FST)

Measured with blue and red light

Month 3 Mean (SEM)

- Change from baseline (Log,10 photo- cd/m²)
- Improvement

Blue
- Treated Eye
- Blue
- Contralateral Eye
Red
- Treated Eye
- Red
- Contralateral Eye
Best Corrected Visual Acuity (BCVA)

ETDRS
(LogMAR -0.3 - 1.6)

BRVT
(LogMAR 1.4 - 4.0)
Best Corrected Visual Acuity (BCVA)

Majority of subjects had clinically meaningful improvement

3 Months mean (SEM) and Median

-3.0
-2.5
-2.0
-1.5
-1.0
-0.5
0.0
0.5
Mean
Median
Mean
Median
Treated (N=8)
Contralateral (N=8)

Individual subject responses

Clinically meaningful (-0.3 LogMAR)

Change from baseline (LogMAR)

p=0.011
Sepofarsen time-to-onset of response was similar for FST and BCVA

BCVA improvement appears to be more rapid than with Luxturna®

Mobility course

Improved at month 3 and month 6

Month 3 Mean (SEM)

Mean change from baseline through month 6

Clinically Meaningful (2 levels)

Treated Eye | Contralateral Eye | Individual subject responses

Treated (N=7) | Contralateral (N=7)

Baseline (N=9) | M3 (N=7) | M6 (N=4)
Discussion of evolving safety findings in trial PQ-110-001

- At the time of the IA, no significant, unanticipated AEs had been reported.

- Subsequently, lens opacities and CME were observed in a dose- and time-dependent manner:
  - Lens opacity occurred approx. 4 months earlier in mid dose group compared to low dose group, with none observed prior to month 4;
  - CME only observed in mid dose group (3-4 months into the study)

- Investigators judged that 3 of 6 lens opacities required surgical removal
  - 2 subjects had demonstrated improved BCVA prior to developing the cataract. After surgery restoration of benefit was observed.

- Both subjects with CME were judged to be mild in severity and not associated with reduced visual acuity.
  - Both started on standard of care treatment with partial resolution noted on one month follow-up OCT

- Dose modifications and longer dosing interval introduced in program:
  - After 12 month visit, all subjects will be rolled over into an extension trial with every six month treatment with the low dose regimen.
Study PQ-110-003 proposed dose regimens

Modeling based on estimated $t_{1/2}$ in retina 200d from NHP

**Low dose pivotal**
(80 $\mu$g load/40 $\mu$g maintenance*)

- CME Risk
- Lens opacity Risk

**Primary dose pivotal**
(160 $\mu$g load/80 $\mu$g maintenance*)

- CME Risk
- Lens opacity Risk

*Every 6 months after 3 month dose

[Graph showing exposure relative to maximum vitreous exposure over time for low and primary dose pivotal regimens.]
Study PQ-110-003 proposed dose regimens

Efficacy is predicted in low dose regimen

Low dose pivotal
(80 µg load/40 µg maintenance*)

Expression levels (%)

<table>
<thead>
<tr>
<th>QR-110 (µM)</th>
<th>0.3</th>
<th>1</th>
<th>3</th>
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<tbody>
<tr>
<td>26-X-27</td>
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<td>***</td>
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<tr>
<td>26-27</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

Lens opacity Risk
CME Risk

Dose (µg): 80 40 40

*Every 6 months after 3 month dose

CEP290 exon skipping in organoid

Exposure relative to maximum vitreous exposure

Dose (µg):

Low dose
Primary dose

ProQR Therapeutics – R&D Day 2019
**Pivotal Phase 2/3 trial**

*Design agreed on with FDA*

- Double-masked, randomized, controlled, 12-month, multiple dose study
- Could serve as the sole registration trial
- Sites in North America and select EU countries
- 30+ patients >8 years old
- Multiple IVT injections in both eyes
- Expected to start H1 2019
- Primary (registration) endpoint:
  - Visual acuity (ETDRS, BRVT)
- Key secondary endpoints
  - Mobility course
  - Full field stimulus testing (FST)
  - Ocular instability (OCI)
  - Optical coherence tomography (OCT)

---

![Trial Timeline](image)

- **sepofarsen**: 160 µg loading dose, 80 µg maintenance dose (n=10)
- **sepofarsen**: 80 µg loading dose, 40 µg maintenance dose (n=10)
- Sham-procedure (n=10)

= Dose first eye  = Dose second eye
**QR-421a for Usher syndrome**

*Designed to treat genetic vision loss in Usher and non-syndromic RP*

### Usher

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

### Partnership

- Awarded $7.5M financial support from FFB to conduct trial

### Unmet need

- For USH2A exon 13 no therapy available

### ✔️

- RNA is established modality in eye
- Strong preclinical proof of concept in patient retinal model
- Orphan drug designation
- Fast track designation
- IND approved by FDA

### STELLAR Phase 1/2 trial

- Expect to dose a first patient with QR-421a in Q1 2019 with safety and efficacy results in mid-2019
- Expect results from multiple dose adaptive trial YE 2020
Molecular rationale is similar in Ush2a and LCA10

QR-421a primarily targets rod restoration
Similar retinal organoid molecular activity of QR-421a and sepofarsen

Lower starting dose in QR-421a Phase 1/2 program

QR-421a-treated optic cups
From Usherin c.2299delG homozygous patient

Sepofarsen-treated optic cups
From CEP290 c.2991+1655A>G homozygous patient
Restoration of usherin protein and ERG amplitude in exon 13 mutant zebrafish

<table>
<thead>
<tr>
<th>Usherin protein (in red) in zebrafish retina</th>
</tr>
</thead>
<tbody>
<tr>
<td>With usherin protein</td>
</tr>
</tbody>
</table>

Usherin protein is shown in red. Without usherin protein, the expression is lower, and with treatment, it increases.

![ERG with light stimulus in zebrafish](image)

**ERG with light stimulus in zebrafish**

- **Wild-type range**

- Exon 13 mutant zebrafish without treatment
- Treated exon 13 mutant zebrafish

Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands
Pharmacokinetics in non human primates
Rapid clearance from vitreous with prolonged retention and activity in retina

---

**Pharmacokinetics**

**Retina**

![Graph showing mean concentration (µg/g) over days for different doses of QR-421a in the retina.]

**Vitreous humor**

![Graph showing mean concentration (µg/ml) over days for different doses of QR-421a in the vitreous humor.]

- 19µg/eye QR-421a
- 72µg/eye QR-421a
“Read-through” from LCA10 to Ush2a

- CEP290 and Usherin are co-localized in photoreceptors
- Sepofarsen and QR-421a have similar concentration-response curves in retinal organoids
- QR-421a has additional preclinical translational PoC in animal model

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Cellular MoA</th>
<th>Target cell</th>
<th>Active in retinal organoid</th>
<th>Active in animals</th>
<th>Active in humans</th>
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</thead>
<tbody>
<tr>
<td>sepofarsen</td>
<td>Restore cilium and OS</td>
<td>Photoreceptor Cones</td>
<td>Yes ≤1μM</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>QR-421a</td>
<td>Restore cilium and OS</td>
<td>Photoreceptor Rods</td>
<td>Yes ≤1μM</td>
<td>Yes</td>
<td>TBD</td>
</tr>
</tbody>
</table>
Key trial goals/objectives

• Establish safety and pharmacokinetics
• Identify dose/duration for next study
• Assess efficacy based on:
  • Improvement in visual fields, particularly rod function
  • Evidence of structural improvement consistent with VF improvement as measured by OCT
  • Other functional vision improvements
Usher Syndrome clinical disease progression

Hearing impairment

Loss of visual field (rod degeneration)

Complete blindness (rods and cones degenerated)

AGE* (YEARS)

High within patient variability in onset and progression of disease

Night blindness (start rod degeneration)

Loss of central vision (cone degeneration)

Initial study population (FIH)

Expanded study population (Ph2/3)
Area of recoverable function in Ush2a localized by OCT in early and advanced disease

ProQR Therapeutics – R&D Day 2019
Visual field defects

Normal Visual Field

Usher syndrome

- Earlier stage disease
- Later stage disease
Primary efficacy measures:
Quantifying visual field defects and EZ-line extension

Earlier stage disease
Later stage disease
Potentially viable photo-receptors as shown by OCT
Indicates potential area of visual functional restoration by QR-421a

OCT: Extension of EZ Change in ellipsoid zone
Macula EZ plus peripheral extension
**QR-421a Phase 1/2 trial in Usher 2a patients**

**STELLAR Phase 1/2 trial**
- Single dose, double-masked, randomized, controlled trial
- Goals include safety and efficacy PoC and dose interval
- ~18 adult patients with moderate to severe eye disease
- Inclusion criteria: visual field of $>10^\circ$, visual acuity of 20/32 or worse

---

Single intravitreal injection in one eye, or sham treatment (randomized 2:1 active:control per cohort)
- Key trial endpoints: Visual field (Medmont DAC Perimetry, Static VF, microperimetry) and OCT
- IND open, data expected in mid-2019

---

Meeting of independent DSMC
Break

Presentations to start again at 10am ET
Thaddeus (Ted) Dryja, MD

- **Professor of Ophthalmology** at Harvard Medical School and at the Massachusetts Eye and Ear Infirmary
- Previously **Global Head of Ophthalmology Research** at the Novartis Institutes for Biomedical Research
- Research in **molecular genetics** of hereditary diseases of the retina
- **Research discoveries** include the identification of the genes responsible for forms of retinal degeneration and dysfunction
- Member of the **U.S. National Academy of Sciences**
Therapeutic History of Ophthalmology

Thaddeus (Ted) Dryja, MD
Professor of Ophthalmology Harvard Medical School, Faculty member at the Massachusetts Eye and Ear Infirmary
2000: First therapy for neovascular age-related macular degeneration started a multi-billion-dollar company (QLT)

Visudyne: a photosensitizing dye is given intravenously and a laser photocoagulates the abnormal vessels

Visual acuity (mean)

2004: Second therapy for neovascular age-related macular degeneration started another multi-billion-dollar company (Eyetech)

Macugen (anti-VEGF aptamer)

Visual acuity (mean)

Macugen injections given every 6 weeks

2006: Lucentis considered a miracle drug because it produced an average gain in vision; drugs in this class have sales over $5B/year

Baseline acuity = 20/90

Final acuity = 20/69

Final acuity = 20/174

Lucentis: anti-VEGF Fab administered as an intravitreal injection

Despite the dramatic mean improvement, 60% of ranibizumab-treated eyes end with vision less than 20/40
Key need in ophthalmology: prevent blindness

- Macular degeneration: 59%
- Glaucoma: 8%
- Diabetic retinopathy: 6%
- Hereditary retinal disorders: 5%
- Optic atrophy: 4%
- Disorders of visual cortex: 2%
- Stroke: 2%
- Retinal vein occlusion: 2%
- Myopia: 1%
- Unknown cause: 3%
- Other: 8%
- Diabetic retinopathy: 6%
- Glaucoma: 8%

A patient’s perspective: Gordon Gund (founder and co-chairman of the Foundation Fighting Blindness)
Normal human fundus (left eye)

Fundus of patient with retinitis pigmentosa (left eye)

1. Attenuated blood vessels
2. Bone-spicule-shaped intraretinal pigment deposits
3. Pale optic nerve head
Gross dissection of eyes from patients with retinitis pigmentosa obtained at autopsy
Normal retina from:
https://library.med.utah.edu/WebPath/HISTHTML/NORMAL/NORM013.html
Normal retina

- Nerve fiber layer
- Ganglion cells
- Bipolar, horizontal amacrine, etc.
- Rod and cone photoreceptors
- Retinal pigment epithelium

Region of severe degeneration in retinitis pigmentosa

- Intraretinal pigment deposits
  - No longer identifiable

Normal retina from:
https://library.med.utah.edu/WebPath/HISTHTML/NORMAL/NORM013.html
Inheritance patterns in retinitis pigmentosa (including Usher syndrome and Bardet-Biedl syndrome)
Autosomal dominant retinitis pigmentosa, 30 - 40% of cases

Autosomal recessive retinitis pigmentosa, 50 - 60% of cases

X-linked retinitis pigmentosa, 5 - 15% of cases
Most prevalent RP genes in the United States

Rhodopsin: 25% of dominant RP; 10% of all RP

RPGR: 80-90% of X-linked RP; 8-9% of all RP

USH2A: >17% of recessive RP; >8.5% of all RP

RHO + RPGR + USH2A = 27% of all RP
Electroretinograms (ERGs) in patients with dominant retinitis pigmentosa due to the rhodopsin mutation Pro23His.
Diverse development focus for retinitis pigmentosa: (a “focus” or a “shotgun approach”?)  
Review of clinicaltrials.gov (January, 2019)

<table>
<thead>
<tr>
<th>Low molecular weight</th>
<th>Alternative medicine</th>
<th>Gene therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-dopa</td>
<td>Acupuncture</td>
<td>RLBP1</td>
</tr>
<tr>
<td>inhaled oxygen</td>
<td>Electro-acupuncture</td>
<td>PDE6B</td>
</tr>
<tr>
<td>valproic acid</td>
<td>Exercise</td>
<td>RPGR</td>
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<tr>
<td>N-acetylcysteine</td>
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<td>RPE65</td>
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<tr>
<td>brimonidine</td>
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<td>REP1</td>
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<td>9-cis b-carotene</td>
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<td>Myo7A</td>
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<tr>
<td>Biologics</td>
<td></td>
<td>Optogenetic payload</td>
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<tr>
<td>QR-421A, QR-110 (ProQR-Ush2A)</td>
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<td>CNTF</td>
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<td>rhNGF</td>
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<td>Dietary</td>
<td>Electronic</td>
<td>Cell therapy</td>
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<td>Goji berries</td>
<td>Retinal implants</td>
<td>Bone marrow-mesenchymal cells</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Transcorneal stimulation</td>
<td>given intravitreally or subretinally</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retinal progenitor cells</td>
</tr>
</tbody>
</table>
Vitamin A supplement for retinitis pigmentosa: possible benefit based on a single “phase III” trial

Berson EL et al., Arch. Ophthalmol. 111:761-772, 1993

~ 160 patients/arm enrolled;

However, only ~ 60 patients/arm followed through years 5-6.
Valproic acid for retinitis pigmentosa: anecdotal benefit in 2011 followed by disappointing consequences

2011:
Change in visual field
Oral valproic acid x 3 months

2012:
Oral valproic acid x 4 months

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Eye</th>
<th>Baseline Snellen BCVA</th>
<th>Final Snellen BCVA</th>
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</thead>
<tbody>
<tr>
<td>8.2</td>
<td>OD</td>
<td>20/70</td>
<td>LP</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>20/80</td>
<td>HM</td>
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<tr>
<td>15.6</td>
<td>OD</td>
<td>20/160</td>
<td>20/300</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>20/200</td>
<td>20/600</td>
</tr>
<tr>
<td>34.6</td>
<td>OD</td>
<td>20/300</td>
<td>20/400</td>
</tr>
<tr>
<td></td>
<td>OS</td>
<td>CF 5’</td>
<td>CF 4’</td>
</tr>
</tbody>
</table>


2018:
90 patients, 50:50 randomization, 12 months of therapy: “small but statistically significantly worse outcome for the valproic acid group”

Birch DG et al., JAMA Ophthalmol. 136:849-856, 2018
How the ProQR therapies are addressing unmet need in inherited retinal blindness

Vanguard program:

- QR-110 for Cys998X mutation in CEP290 (congenital retinal blindness)

Successor programs in two of the most prevalent forms of retinitis pigmentosa:

- QR-421 for mutations in exon 13 of USH2A (Usher syndrome 2A)
- QR-411 for c.7595-2144A>G mutation in USH2A (Usher syndrome 2A)
- QR-1123 for the Pro23His mutation in the rhodopsin gene (dominant RP)
  - Knock-down of mutant allele allowing normal allele to serve retina
  - (Heterozygotes for a rhodopsin null allele have vision throughout life)
Creating Medicines

Early Development Pipeline

Peter Adamson, Ph.D., Head of Ophthalmology Research
# ProQR Ophthalmology pipeline

<table>
<thead>
<tr>
<th></th>
<th>DISCOVERY</th>
<th>PRECLINICAL DEVELOPMENT</th>
<th>PROOF OF CONCEPT TRIALS</th>
<th>LATE STAGE/REGISTRATIONAL TRIALS</th>
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</thead>
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<tr>
<td><strong>Ophthalmology</strong></td>
<td></td>
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</tr>
<tr>
<td>Sepofarsen (QR-110) for LCA10 p.Cys998X</td>
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<tr>
<td>QR-421a for Usher syndrome 2A exon 13</td>
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<tr>
<td>QR-1123 for P23H adRP - <em>discovered by Ionis</em></td>
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<tr>
<td>QR-504 for FECD3</td>
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<tr>
<td>QR-411 for Usher syndrome 2A PE-40</td>
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<tr>
<td>QR-1011 for Stargardt's disease c.5461-10T&gt;C</td>
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<tr>
<td>QRX-461 for Usher syndrome undisclosed mutation</td>
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<tr>
<td>QRX-136 for LCA undisclosed mutation</td>
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</tbody>
</table>
QR-1123 for P23H adRP

Gapmer targeting autosomal dominant RP due to the P23H mutation in RHO

**P23H adRP**
- Progressive reduction in night & peripheral vision. Blindness is frequent in mid-adulthood
- No therapy available
- ~2,500 patients with P23H adRP in United States

**QR-1123**
- **Goal:** Restore vision/prevent vision loss in patients with P23H adRP
- Locally administered in the eye. Routine intravitreal procedure
- Anticipated infrequent dosing of 4 times a year or less

**Established modality in eye**
- Strong preclinical proof of concept in vivo
- In-licensed from Ionis Pharmaceuticals
- Majority of IND enabling activities completed
- 2 year Natural History Study is completed and will be used to accelerate clinical development

**Next steps**
- Phase 1/2 trial expected to start in 2019
- Clinical development similar to QR-421a
QR-1123 is specific for P23H allele

Strong and specific suppression of P23H in cells

QR-1123 is selective for P23H in vivo

![Graphs showing suppression of P23H in cells and in vivo.]
QR-1123 preserves ONL and improves ERG in P23H rat model

<table>
<thead>
<tr>
<th>QR-1123 surrogate preserves ONL in P23H Tg rat</th>
</tr>
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<tbody>
<tr>
<td>mRHO AS03</td>
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<tr>
<th>QR-1123 surrogate improves ERG in P23H Tg rat strong correlation with ONL preservation</th>
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<tbody>
<tr>
<td>QR-1123 surrogate</td>
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</table>

Murray et al., 2015 IOVS 56: 6362
QR-1123 reduces retinal degeneration in humanized P23H mice
Overview: QR-1123 for P23H adRP

mRNA profile restoration
- Increase in rhodopsin mRNA profile and reduction in mutant mRNA
- Strong selectivity for mutant over WT mRNA

Local (intravitreal) delivery to the eye
- Eye well validated target for oligos
- Efficient delivery to photoreceptor layer in the retina

Evidence of improvement in photoreceptors
- Evidence of functional improvement (ERG) in knock-in Tg mice
- Evidence of histological protection in human P23H opsin KI mouse

Clinical candidate selected
- QR-1123 selected as clinical candidate

Development
QR-411 for Usher syndrome

*Designed to treat genetic eye disease in Usher syndrome*

**Usher**
- Develop hearing loss and blindness in childhood and turn completely blind by mid adulthood
- PE40 mutation affects ~1,000 patients in Western world

**QR-411**
- For Usher PE40 no therapy available
- RNA is established modality in eye
- Strong preclinical proof of concept in patient retinal organoids
- Orphan drug designation

**Strong PoC**
- Strong preclinical PoC in human organoid models. Development candidate selected

**Next steps**
- IND-enabling studies expected to start in 2019
- Clinical development similar to QR-421a
QR-411 for RP in Usher syndrome

Splice correction for PE40 USH2A mRNA

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

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

Exclusion of PE40 from the mRNA leads to wild-type Usherin protein.

Identical molecular mechanism to sepofarsen - splice correction creating WT mRNA
QR-411 for Usher syndrome
USH2A PE40 splice correction

**QR-411 - Clinical Development**
- Design and endpoints very similar to that for QR-421a (RP) and QR-1123 (adRP)

**QR-411 - Asset Characterization**
- Single stranded 20-mer RNA oligonucleotide
- Chemically modified for stability, safety, efficiency and uptake
- Well understood MoA
- Designed to target the USH2A PE40 mutation
- IVT administration, based on studies with LCA sepofarsen likely no detectable systemic exposure in animals

**QR-411 - Data**
- >95% effect in mediating Ush2A PE40 mRNA in patient derived fibroblasts and optic cups
- Ability to edit human Ush2A PE40 mRNA in human knock-in transgenic fish
- Ability to distribute to photoreceptor layer after IVT injection
- Initial tolerability studies in rabbits shows similar profile to sepofarsen
In vitro proof of concept

Dose-dependent effect of QR-411 on WT RNA in patient fibroblasts

Efficacy testing of QR-411 in heterozygous patient fibroblasts

- Sepofarsen showed similar responses in LCA patient fibroblasts
- Similar data for QR-411 in PE40 het retinal organoids at 2uM and 10uM concentrations (cf same efficacy range as sepofarsen approx. 100%)
In vitro proof of concept
QR-411 restores WT RNA in patient-derived iPSC optic cups

Healthy control
Ctrl 2µM  Ctrl 10µM  QR-411 2µM  QR-411 10µM
Patient (PE40 heterozygous)
Ctrl 10µM  QR-411 2µM  QR-411 10µM  Neg. Ctrl

Exon 40  PE40  Exon 41
Exon 40  Exon 41

Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands
Overview: QR-411 for USH2A PE40

- **mRNA profile restoration**: mRNA profile restored to wild-type

- **Local (intravitreal) delivery to the eye**: Eye well validated target for oligos. Efficient delivery to outer nuclear layer in the retina

- **mRNA profile restoration in optic-cups**: mRNA profile shows PE40 skip in patient-derived optic cups retinal organoids

- **Clinical candidate selected**: QR-411 selected as clinical candidate

- **Development**
QR-1011 for Stargardt’s disease

Stargardt’s disease

- Develop blindness in childhood and turn completely blind by mid adulthood
- ~7,000 patients with c.5461-10T>C in ABCA4 in Western world

QR-1011

- For Stargardt’s c.5461-10T>C in ABCA4 no therapy available
- RNA is established modality in eye
- Strong pre-clinical proof of concept

Strong PoC

- Preclinical PoC and efficacy in human mini-gene models

Next steps

- Progression into retinal organoid
Stargardt’s disease: clinical phenotype

- Most frequent form of inherited juvenile macular degeneration
- Manifests as central vision loss and progresses to complete blindness
- Median onset of disease approx. 17 years
- Loss of RPE cells (scotoma)
Prevention of Exon 39 exclusion

Splice correction
QR-1011 screening

Next Steps is to optimize in human ABCA4 c5561-10C>T retinal organoids ‘optic cups’
**Ophthalmology: QR-1011 for Stargardt’s disease**

**QR-1011 drives splice correction of mutant ABCA4 mRNA**
- Ex39 inclusion demonstrated in mutant ABCA4 mutant mini-gene construct upon treatment with a number of oligo sequences

**Cells isolated from patient ABCA4 c.5461-10T>C**
- Renal epithelial cell already isolated from patient urine. Cells will begin re-programming into optic cups

**Local (intravitreal) delivery to the eye**
- Eye well validated target for oligos
- Efficient delivery to photoreceptors (ONL)

**QR-1011 profiling in retinal organoids**
- Ex39 exclusion to be confirmed in ABCA4 c5461-10T>C and restoration with QR-1011 in retinal organoids to be confirmed

**QR-1011 chemistry optimization**
- Chemistry/sequence optimization ongoing

---

ProQR Therapeutics – R&D Day 2019
QR-504 for FECD3

Fuchs Endothelial Corneal Dystrophy

Front of the eye disease leading to blindness in 50+ years of age

>250,000 patients with Repeat expansion in TCF4 in Western world

QR-504

For FECD3 repeat expansion in TCF4
No therapy available

Strong PoC

Strong preclinical PoC in human primary cell models. Development candidate selected

✓ RNA is established modality in eye
✓ Rapid delivery to corneal cells
✓ Strong preclinical proof of concept in human primary cell models

Next steps

• Progression into development
Clinical phenotype: Fuchs Endothelial Corneal Dystrophy

- Late onset (50-60 years) slowly progressing corneal dystrophy that usually affects both eyes
- Patients often awaken with blurred vision which improves during the day
- Visual acuity reduction
- Finally corneal swelling and clouding often requiring corneal transplantation
**QR-504 for FECD3**

*TCF4 repeat targeting for reduction of RNA foci*

In healthy cells, MBNL1 protein regulates splicing of many RNAs.

Mutated TCF4 RNA forms aggregates (foci) and sequesters MBNL1, disrupting splicing processes.

QR-504 targets the TCF4 RNA (foci) and releases MBNL1 to enable correct splicing of RNA.
QR-504 for FECD

QR-504 - Clinical Development
- ‘Molecular PoC” in human corneal endothelial cells derived from FECD patients undergoing corneal transplant surgery

QR-504 - Asset Characterization
- Single stranded 21-mer RNA oligonucleotide
- Sequence and chemistry fully optimized.
- Chemically modified for stability and uptake
- Well understood MoA
- Designed to target nucleotide expansion in FECD3 patients caused by mutations in the TCF4 gene
- IVT administration, no detectable systemic exposure

QR-504 - Data
- Human TNR expanded TCF4 FECD3 CECs shown to have RNA foci and QR-504 treatment reduces foci
- Human TNR expanded TCF4 FECD3 CECs shown to have MBNL-1 sequestered with RNA foci and QR-504 treatment releases MBNL-1
- Well understood MoA
- IVT administration shows QR-504 uptake in CECs from mouse and rabbit
FECD patients with TCF4 mutations have RNA foci

FECD is caused by toxic RNA aggregation and MBNL-1 sequestration

### Control

<table>
<thead>
<tr>
<th>TCF4</th>
<th>Free MBNL1</th>
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<tr>
<td><img src="image1" alt="CAG7-Cy3" /></td>
<td><img src="image2" alt="MBNL1" /></td>
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### FECD

<table>
<thead>
<tr>
<th>Mutant TCF4</th>
<th>MBNL1</th>
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<tbody>
<tr>
<td><img src="image3" alt="CAG7-Cy3" /></td>
<td><img src="image4" alt="MBNL1 (CAG7-Cy3)" /></td>
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### Article

**Antisense Therapy for a Common Corneal Dystrophy Ameliorates TCF4 Repeat Expansion-Mediated Toxicity**

Christina Zarouchi,1,8 Beatriz Sanchez-Pintado,1,8 Nathaniel J. Hafford Teur,1,8 Pontus Klein,2 Petra Liskova,3,4 Kalyan Dulla,2 Ma’ayan Semo,1 Anthony A. Vugler,1 Kirithika Muthusamy,1,5 Lubica Dudakova,2 Hannah J. Lewis,6 Pavlina Skalicka,3,4 Piro Hysi,7 Michael E. Cheetham,1 Stephen J. Tuft,1,5 Peter Adamson,2,9 Alison J. Hardcastle,1,9 and Alice E. Davidson1,5,9

ProQR Therapeutics – R&D Day 2019
FECD patients with TCF4 mutations have RNA foci

FECD is caused by toxic RNA aggregation and MBNL-1 sequestration
QR-504 reduces toxic foci

Ctrl AON

QR-504

Mann-Whitney

p = 0.002165

QR-504 reduces foci in patient CECs (N=6)

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QR-504 reduces toxic foci and MBNL-1 sequestration

Patient #202, CTG 12,96
IVT administered QR-504 shows robust delivery to corneal endothelium

Cy3-labelled QR-504, 48h post dose, 10ug IVT dose
Ophthalmology: QR-504 for FECD

QR-504 reduces toxic foci
mRNA of toxic foci removed upon QR-504 treatment of primary corneal endothelial cells of FECD patients

QR-504 reduces sequestration of MBNL-1
MBNL-1 sequestration is reduced upon QR-504 treatment of primary corneal endothelial cells of FECD patients

Local (intravitreal) delivery to the eye
Eye well validated target for oligo's
Efficient delivery to corneal endothelium

Development
# ProQR Ophthalmology pipeline

<table>
<thead>
<tr>
<th>Ophthalmology</th>
<th>DISCOVERY</th>
<th>PRECLINICAL DEVELOPMENT</th>
<th>PROOF OF CONCEPT TRIALS</th>
<th>LATE STAGE/REGISTRATIONAL TRIALS</th>
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<tbody>
<tr>
<td>Sepofarsen (QR-110) for LCA10 p.Cys998X</td>
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<td>QR-421a for Usher syndrome 2A exon 13</td>
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<td>QRX-461 for Usher syndrome undisclosed mutation</td>
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<tr>
<td>QRX-136 for LCA undisclosed mutation</td>
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Innovation at ProQR
From LCA10 to 10 LCA’s per year...

Gerard Platenburg, Chief Innovation Officer
Building from the current ophthalmology programs

*Reaching patients beyond p.Cys998X mutation*

<table>
<thead>
<tr>
<th>Deep</th>
<th>Broad</th>
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<tbody>
<tr>
<td><strong>CEP290, USH2A</strong></td>
<td><strong>LCA</strong></td>
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<tr>
<td>Targeting additional CEP290, USH2A mutations which are not targeted by sepofarsen, QR-421a and QR-411</td>
<td>At least 24 genes other than CEP290 results in LCA</td>
</tr>
</tbody>
</table>

- Broadening beyond LCA and Ush2a
- ~300 inherited retinal disorders
RNA technology toolbox

One therapeutic modality using different MoAs

One modality—Variety of mechanisms
Antisense oligonucleotides, chemically modified to enhance uptake and increase stability
QRX-136 for LCA10

LCA10

- Lose sight in first years of life
- No therapy available

QRX-136

- **Goal:** Restore vision/ prevent vision loss in patients with LCA10
- RNA is established modality in eye
- Strong preclinical proof of concept

- Locally administered in the eye. Routine intravitreal procedure
- Anticipated infrequent dosing of 2 times a year

- **Undisclosed** mutation in CEP290 affecting ~500 patients in Western world*

**Next steps**

- Progression into lead selection
- Development following sepofarsen in well defined development plan

*Number based on initial prevalence assessment
QRX-136 for LCA10

In vitro efficacy of AONs

- Several AONs identified that efficiently skip CEP290 exon 36
- Over 50% exon skip is observed
- Lead optimization is ongoing
QRX-461 for Usher syndrome
Designed to treat genetic eye disease in Usher syndrome 2a

Usher
Develop hearing loss and blindness in childhood and turn completely blind by mid adulthood

Undisclosed mutation in USH2A affecting ~5,000 - 10,000 patients in Western world*

QRX-461
No therapy available

Strong PoC
Strong preclinical PoC in vitro models. Development candidate selection ongoing

☑ RNA is established modality in eye
☑ Strong preclinical proof of concept
☑ QRX-461 is based on Axiomer® technology

Next steps
• Progression into lead selection
• Development following QR-421a and QR-411 in well defined development plan

*Number based on initial prevalence assessment
Axiomer® technology

Therapeutic oligonucleotides for directing site-specific A-to-I editing by endogenous ADAR enzymes
Axiomer® Editing Oligonucleotides (EONs)

Oligonucleotide mediated targeted RNA editing

- Unique RNA editing technology
- Applicable to >20,000 disease-causing mutations
- Similar capabilities as CRISPR, without the key risks
- Brings clinical applicability of “editing” in reach
- IP fully owned ProQR far ahead of competition
- In-vitro PoC established in multiple disease models
A-to-I editing: Therapeutic opportunity

The most prevalent editing event in human tissues

- No sequence dependence
- 4 million A-to-I sites in the human transcriptome, both in coding and non-coding RNAs
- Extent of editing similar in most human tissues, making therapeutic editing feasible in all disease areas

- ADAR1 and ADAR2 expressed in retina
- >20,000 G-to-A disease causing mutations in genome
- >1,100 G-to-A disease causing mutations in retinal genes
- ~90 G-to-A mutations found in Ush2a

Adapted from Protein atlas
EONs designed for targeted editing

ADAR deaminates target A in EON-target RNA helix
EONs designed for targeted editing

Advantage over RNA guides: Specificity

Endogenous editing

Editing site with RNA guides is flexible

EON-directed therapeutic editing

Editing site with EONs is precise:
No off-target editing even if ADAR shifts
Structural basis for nt modifications

ADAR binding and catalysis require different modifications

ADAR binding region
- Modifications compatible with ADAR binding, but which do not fit in the catalytic center

Editing enabling region
- Modifications that fit into the catalytic center

Structural modelling provides a basis for further optimization of EONs
EONs edit *Idua* mRNA *in vitro*

*Idua* W392X reporter construct in MEF cells with endogenous ADAR

Sanger sequencing

Non-treated  EON 1 (100 nM)  EON 2 (100 nM)

Digital droplet PCR (% edited *Idua* mRNA)
EONs restore iduronidase *in vitro*

Idua W392X reporter construct in MEF cells with endogenous ADAR

Proteins from EON-treated cells

Incubation with fluorescent iduronidase substrate analog

Fluorescent readout

![Iduronidase activity (Fold-change over ctrl)](image-url)
Nt modifications ensure specificity

Editing only observed at the target adenosine, even when overexpressing ADAR in cells

- 100 nM EON transfection with GFP W57X reporter and ADAR1 overexpression
- Readout by Sanger sequencing of the RT-PCR product
- ~85% editing at target A; no off-target editing observed
PoC in Hurler mouse model for targeted editing

Readouts for restored function in IDUA Hurler mouse model

RNA sequence correction

Enzymatic activity

GAG accumulation

Enzymatic activity (% change over control)

GAG reduction (% change over control)
Axiomer® is widely applicable

Examples of ophthalmic targets

CNS (>500 targets)
- Parkinson's Disease VIII
- Hurler Syndrome
- Alzheimer's Disease
- Huntington's Disease
- Parkinson's Disease II
- Fragile X syndrome

Lung (>300 targets)
- Cystic Fibrosis non-dF508
- Primary ciliary dyskinesia
- Surfactant Metabolism Dysfunction
- ABCA3 deficiency
- Familial Pulmonary Fibrosis

Skin (>500 targets)
- Albinism
- Dystrophic Epidermolysis Bullosa
- Junctional Epidermolysis Bullosa
- Darier disease
- Epidermolysis Simplex

Ophthalmology (>1,100 targets)
- Leber's Congenital Amaurosis 4
- Usher's syndrome
- Fuchs Endothelial Corneal Dystrophy
- Retinitis Pigmentosa type 3
- Stargardt's Disease
- Primary Congenital Glaucoma

Liver (>1,500 targets)
- Alpha-1 Antitrypsin Deficiency
- Factor V Deficiency
- Transthyretin-related hereditary amyloidosis
- Wilson disease
- Hereditary Hemochromatosis
- Ornithine Transcarbamylase deficiency
- Hemophilia B
- Pompe Disease

ProQR Therapeutics – R&D Day 2019
QRX-461 for Usher syndrome

**Designed to treat genetic eye disease in Usher syndrome 2a**

**Usher**

- Develop hearing loss and blindness in childhood and turn completely blind by mid adulthood

**Undisclosed** mutation in USH2A affecting ~5,000 - 10,000 patients in Western world*

**QRX-461**

- No therapy available

**Strong PoC**

- Strong preclinical PoC in vitro models
- Development candidate selection ongoing

- RNA is established modality in eye
- Strong preclinical proof of concept
- QRX-461 is based on Axiomer® technology

**Next steps**

- Progression into lead selection
- Development following QR-421a and QR-411 in well defined development plan

*Number based on initial prevalence assessment*
QRX-461 corrects G-to-A mutation

In vitro efficacy of AONs

- Several EONs designed for Usherin exon 61
- Up to 50% editing is observed
- Optimization is ongoing