QR-421a: An antisense oligonucleotide for the treatment of RP due to USH2A exon 13 mutations

11th Annual USH Connections Conference
Philadelphia, 13th July 2019

Aniz Girach, MD
Chief Medical Officer, ProQR Therapeutics
Forward looking statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including but not limited to, statements regarding our strategy, future operations, future preclinical and clinical trial plans and related timing of trials and results, research and development, future financial position, future revenues, projected costs, prospects, therapeutic potential of our product candidates, plans and objectives of management, are forward-looking statements. The words “aim,” “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

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Eye is ideal for RNA (antisense oligonucleotide—ASO) therapeutics

Small Compartment

Visible & Accessible

Relative Immuno-privileged Site
- Blood-retina barrier, tight cell junctions
- Local immunomodulatory factors present
- Scarcity of antigen presenting cells

Target Rich
- 300 Known genetic causes of blindness
- 220 Mapped to specific gene

Facilitated by imaging systems, e.g. OCT machines
How we see:

1. Light entering eye triggers photochemical reaction in rods and cones at back of retina.

2. Chemical reaction in turn activates bipolar cells.

3. Bipolar cells then activate the ganglion cells, the axons of which converge to form the optic nerve. This nerve transmits information to the visual cortex in the brain’s occipital lobe.

Human retina. Courtesy Rowland Hall
Inherited Retinal Disease (IRD) management: coming of age

- Improved genetic 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 antisense oligonucleotide (ASO) drugs compare with gene therapy?

<table>
<thead>
<tr>
<th>RNA Antisense 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>
The Opportunity in Inherited Retinal Diseases

RNA Therapeutics 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 in Inherited Retinal Diseases

>300 genes causing Inherited Retinal Diseases, described with >50 pathogenic mutations per gene, leading to >15,000 targets.

RNA Therapeutics characteristics, irrespective of the target

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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.
The Opportunity in Inherited Retinal Diseases

RNA Therapeutics 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 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>
<td>Sepofarsen (QR-110) for LCA10 p.Cys998X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>QR-421a for Usher syndrome 2A exon 13</td>
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<td></td>
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<tr>
<td>QR-1123 for FZ3H dRP - discovered by Ionis</td>
<td></td>
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<td></td>
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<tr>
<td>QR-504 for FECD3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>QR-411 for Usher syndrome 2A PE-40</td>
<td></td>
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<tr>
<td>QR-1011 for Stargardt’s disease c.5461-107&gt;C</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>QRX-461 for Usher syndrome undisclosed mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>QRX-136 for LCA undisclosed mutation</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Other therapeutic areas**

| QRX-704 for Huntington’s Disease | | | | |

**Spin-out companies**

<table>
<thead>
<tr>
<th>Amylon Therapeutics</th>
<th>AT-010 for HCHWA-D</th>
</tr>
</thead>
</table>

| Wings Therapeutics | QR-313 for DEB exon 73 |
Sepofarsen (QR-110) for Leber’s Congenital Amaurosis Type 10 (LCA10)

LCA10

Lose sight in first years of life

No therapy available

p.Cys998X(CEP 290) 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 ILLUMINATE trial initiated in April 2019; data expected around YE 2020

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# LCA 10 Phase 1/2: Top Line Efficacy Results

Concordant improvement in all key outcome measures

<table>
<thead>
<tr>
<th>Outcome Measure</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>Visual Acuity (ETDRS/BRVT) – LogMAR (n=8)</td>
<td>↓ = improved</td>
<td>≥ -0.3</td>
<td>Treated: -0.67 (0.32) Untreated: 0.02 (0.05)</td>
</tr>
<tr>
<td>Mobility Course – level (n=7)</td>
<td>↑ = improved</td>
<td>≥2</td>
<td>Treated: 2.57 (1.19) Untreated: 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>Treated: -0.74 (0.35) Untreated: -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>Treated: -0.91 (0.38) Untreated: -0.02 (0.11)</td>
</tr>
<tr>
<td>Nystagmus tracking (OCI) - Log₁₀mm (n=7)</td>
<td>↓ = improved</td>
<td></td>
<td>Treated: -0.14 (0.08) Untreated: -0.04 (0.06)</td>
</tr>
</tbody>
</table>
## Similarities between LCA10 and Ush2a

- CEP290 and Usherin are co-localized in the connecting cilium of 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/optic cup</th>
<th>Active in animals</th>
<th>Active in humans</th>
</tr>
</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>
Treatment rationale is similar in Ush2a and LCA10

QR-421a primarily targets rod restoration
Usher Syndrome clinical disease progression

- Hearing impairment
- Loss of visual field (rod degeneration)
- Complete blindness (rods and cones degenerated)

*High within patient variability in onset and progression of disease

AGE* (YEARS)

0 10 20 30 40 50 60

Night blindness (start rod degeneration)
Loss of central vision (cone degeneration)
QR-421a for Usher syndrome

Investigative treatment for vision loss in Usher and non-syndromic RP

Usher

- Develop hearing and vision loss in childhood and are completely blind by mid adulthood
- USH2A exon 13 mutations affect ~16,000 patients in Western world

Partnership

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

Unmet need

- For USH2A exon 13 no therapy available

Strong preclinical proof of concept in patient retinal model
- Orphan drug designation
- Fast track designation
- First patient dosed

STELLAR Phase 1/2 trial
- 3 month Interim analysis on first and second cohort expected Q1 2020, including top line safety and efficacy data
QR-421a for RP in Usher syndrome

Skipping of exon 13 in USH2A mRNA

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

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

Exclusion of the exon harboring the mutation leads to restoration of functionality of usherin.
QR-421a mediated USH2A exon 13 skip in optic cups

With QR-421a treatment there may be sufficient “normal” mRNA expression, which can lead to restoration of usherin protein.
Restoration of usherin protein and ERG amplitude in exon 13 mutant zebrafish

<table>
<thead>
<tr>
<th></th>
<th>Usherin protein (in red) in zebrafish retina</th>
</tr>
</thead>
<tbody>
<tr>
<td>With usherin protein</td>
<td>![Image of usherin protein with red color]</td>
</tr>
<tr>
<td>Without usherin protein</td>
<td>![Image of retina without usherin protein]</td>
</tr>
<tr>
<td>Treated with oligo</td>
<td>![Image of treated retina with usherin protein]</td>
</tr>
</tbody>
</table>

ERG with light stimulus in zebrafish

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

With QR-421a treatment, retina appearance and function improved

*Erwin van Wijk, Radboudumc, Nijmegen, the Netherlands*
Pharmacokinetics in non human primates

Rapid clearance from vitreous with prolonged retention and activity in retina

Pharmacokinetics

QR-421a treatment can be treated 2x/yr
QR-421a Phase 1/2 STELLAR trial in Usher 2a patients

**STELLAR Phase 1/2 trial**
- Single dose, double-masked, randomized, sham controlled, first-in-human trial
- Goals include safety, efficacy and dose exploration
- 24m study
- ~18-30 adult patients with moderate to severe eye disease
- Key inclusion criteria: visual field of ≥10°, 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 acuity, visual field (DAC perimetry (Medmont), automated perimetry (Octopus), microperimetry (MAIA) and OCT
- First patient dosed in March 2019, early interim analysis data expected in end of Q12020

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**Phase 1/2 Single Dose Trial**

- **Low dose** (n=4+2 sham)
- **Mid dose** (n=4+2 sham)
- **High dose** (n=4+2 sham)

**Open label extension**
- n=8-12

**Washout informs dosing interval**

**Adaptive Sham Crossover**
- (n=4-6)

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Meeting of independent DSMC
The study population and endpoints

Ranges are illustrative, not exact
The study population and endpoints

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The study population and endpoints

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The study population and endpoints

STELLAR participants baseline:
• ≥10° Visual Field
• Worse than/equal to 20/32

Ranges are illustrative, not exact
The study population and endpoints

**Ranges are illustrative, not exact**

### Visual Acuity in Snellen
- 20/20
- 20/32
- 20/32
- No Light Perception

### Visual Field in Degrees Vision
- 150°
- 20°
- 10°
- 0°

#### STELLAR participants baseline:
- ≥10° Visual Field
- Worse than/equal to 20/32

#### Disease Severity
- **Mild disease**
  - >20° visual field (more than 6mm functional retina on OCT)
  - Limited decline in visual acuity

- **Moderate disease**
  - <20° visual field (less than 6mm functional retina on OCT)

- **Severe disease**
  - Progressed decline in visual acuity

#### Age
- 0 yo
- 80 yo
Some endpoints used in STELLAR (Ph 1/2 Trial)

Partians with moderate disease*

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

Partians with severe disease*

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- OCT(EZ)
- Patient Reported Outcomes

* Defined according to trial criteria
Some endpoints used in STELLAR (Ph 1/2 Trial)

**Patients with moderate disease***

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

**Patients with severe disease***

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- OCT(EZ)
- Patient Reported Outcomes

* Defined according to trial criteria
Full Field Stimulus Test (FST)

All study subjects

- Test of most sensitive part of the retina
  - White light for total retina
  - Blue light for rods (mostly peripheral)
  - Red light for cones (mostly central macula)

**Goal**
Directional improvement in treatment group
Some endpoints used in STELLAR (Ph 1/2 Trial)

*Patients with moderate disease*

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

*Patients with severe disease*

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- OCT(EZ)
- Patient Reported Outcomes

* Defined according to trial criteria
Visual Field (VF)

For moderate patients

- **Static visual field (Octopus)**
  - Measure of visual field in peripheral vision
  - Gold standard in measuring VF
  - Measures visual field with white light only

- **Dark Adapted Chromatic Perimetry (Medmont)**
  - Measure of visual field in peripheral vision
  - Patients are dark adapted prior to measurement
  - Measures visual field at different wavelengths (colors)

**Goals**

Improvement above the noise of the assay and/or improvement in hill of vision analysis
Some endpoints used in STELLAR (Ph 1/2 Trial)

Patients with moderate disease*

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

Patients with severe disease*

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- OCT(EZ)
- Patient Reported Outcomes

* Defined according to trial criteria
Visual Field (VF)

For severe patients

- Micro perimetry (Maia)
  - Measures visual field in the macula (0-20° visual field)
  - Measures visual field with white light

Goals

Improvement above the noise of the assay and/or improvement in hill of vision analysis
Some endpoints used in STELLAR (Ph 1/2 Trial)

* Defined according to trial criteria

Patients with moderate disease*:

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

Patients with severe disease*:

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- **Visual Acuity**
- OCT(EZ)
- Patient Reported Outcomes
Visual Acuity

*Only applicable in severe patients*

**Snellen Visual Acuity**

- Snellen VA chart used in Clinical Practice

**ETDRS/LogMAR Visual Acuity**

- ETDRS Chart used as Gold Standard for assessing VA in Clinical Trials
- Alternative VA scales used for VA with low vision patients

**Goals**

- In responder analysis an improvement of -0.2 LogMAR (2 lines, or 10-letters) is considered meaningful by EMA
- In responder analysis an improvement of -0.3 LogMAR (3 lines, or 15-letters) is considered meaningful by FDA
- Noise of assay is likely 0.1 LogMAR (1 line, or 5-letters)
Some endpoints used in STELLAR (Ph 1/2 Trial)

Patients with moderate disease*

- Full field stimulus (blue, red and white light)
- Static Perimetry (white light) by Octopus device
- Dark Adapted Chromatic Perimetry (color light) by Medmont device
- Patient Reported Outcomes

Patients with severe disease*

- Full field stimulus (blue, red and white light)
- Micro perimetry by Maia device
- Visual Acuity
- **OCT(EZ)**
- Patient Reported Outcomes

* Defined according to trial criteria
Ellipsoid Zone (EZ) on Optical Coherence Tomography (OCT)

- OCT is a non-invasive way of evaluating the retina cross-sectionally
- EZ represents one component of the photoreceptor layer
- EZ is important because:
  - EZ is easily identified on SD-OCT as objective biomarker
  - RP involves photoreceptor death
  - FDA accepts EZ as primary endpoint for trials
  - EZ width/area can be a biomarker for some retinal degenerative diseases e.g., RP (Ref: Birch et al*)
  - Clinically meaningful change=stat significant change from BL compared to Control

*JAMA Ophthalmol. 2013 September ; 131(9): 1143–1150
Summary

• Eye is ideal organ for RNA therapeutics (antisense oligonucleotides-ASO)
• ASO Treatment characteristics are ideal to treat eye diseases
  • Intra-vitreal delivery; relatively long half-life
• Many Inherited Retinal Diseases being investigated using ASO treatment
  • Ph 2/3 for LCA 10
  • Ph 1/2 for Ushers Type 2a(exon 13)
  • Ph 1/2 for Autosomal Dominant Retinitis Pigmentosa(anticipated end 2019)
• Many different endpoints/instruments being explored
• Many companies are working on trials for IRDs

www.proqr.com