THE ROLE OF RNA THERAPIES IN USHER SYNDROME

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VP Clinical Development 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.

Forward-looking statements represent our management’s beliefs and assumptions only as of the date of this presentation. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those that may be described in greater detail in the annual report filed on Form 20-F for the year ended December 31, 2019 that we have filed with the U.S. Securities and Exchange Commission (the “SEC”) and any subsequent filings we have made with the SEC. We have included important factors in the cautionary statements included in that annual report, particularly in the Risk Factors section, and subsequent filings with the SEC that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.
ProQR Therapeutics

Patient-focused RNA THERAPEUTICS platform company, developing drugs for INHERITED RETINAL DISEASES with well understood genetic causality
ProQR Development Programs at a glance

RNA Therapies in Clinical Development:

• Sepofarsen: Leber Congenital Amaurosis type 10 (LCA10)

• QR-421a: Usher Syndrome / non-syndromic Retinitis pigmentosa due Ush2a Exon 13 mutations

• QR-1123: Autosomal-dominant Retinitis pigmentosa due to Rhodopsin (Rho) mutations
The ProQR Journey for patients with Inherited Retinal Diseases (IRDs)

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<thead>
<tr>
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<tbody>
<tr>
<td>• Founding of ProQR</td>
<td>• Shift to Focus on Eye Diseases</td>
<td>• Start of First Clinical Trial: Sepofarsen in</td>
<td>• Clinical programs</td>
</tr>
<tr>
<td>• Initial Focus on rare</td>
<td>• Development Partnerships with Academia on rare</td>
<td>LCA10</td>
<td>advancing with lead</td>
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<td>lung disease (Cystic</td>
<td>genetic eye disease (LCA, RP)</td>
<td>• Expansion of Clinical Programs to RP with Ush2a</td>
<td>program in registration trial</td>
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<tr>
<td>fibrosis)</td>
<td>• Extensive Preclinical Development</td>
<td>mutations and RP due to Rho mutations</td>
<td>• Molecules in pre-critical</td>
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<td></td>
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<td>phase for &gt;25 additional</td>
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<tr>
<td></td>
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<td>mutations causing IRDs</td>
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LCA = Leber congenital amaurosis, RP = Retinitis pigmentosa
ProQR inherited blindness platform

**UNIQUE PLATFORM FOR PRECISION MEDICINE**

1. **Targeted RNA oligo-nucleotide therapies**
2. **Intravitreal delivery is routine procedure in ophthalmology**
3. **Broad distribution allows for targeting of central and peripheral diseases**
4. **Predictive optic cup model**
Validating the ProQR inherited retinal disease platform

Predictive retinal organoid model
RNA therapy platform for IRD

Model-informed drug discovery (MIDD) de-risks and accelerates development

Human retinal organoid model

Response in retinal organoids

Phase 1/2 human trial

ProQR’s Skin to Eye Initiative
Models are generated from small skin punch biopsies from patients with eye diseases
How QR-421a works: exon skipping to remove mutation

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 RNA therapy in USH2A

MIDD predicts clinical response at human dose 50-200µg/eye

Response in retinal organoids

Phase 1/2 Stellar trial, (ongoing)

Interim Analysis Q1 2020

- COHORT 1: 50 µg
  - 4 active, 2 sham

- COHORT 2: 100 µg
  - 4 active, 4 sham

- COHORT 2B: 100 µg
  - Homozygous

- COHORT 3: 200 µg

3 months
QR-421a RNA therapy

For USH2A mediated Usher syndrome and non-syndromic retinitis pigmentosa
How RNA Therapy is administered

Injection of Therapies into the eye ball (“intravitreal”) are routine procedures in ophthalmology

- Infrequent injections, ~2-3 times per year
- No viral vector “carrying” the therapy (“Naked”)

Broad distribution allows for targeting of central and peripheral diseases

- Oligo’s distribute broadly in the eye
- Allowing for targeting central and peripheral disease
Typical Disease Progression in Retinitis Pigmentosa

Mild to Moderate disease

- Night blindness (start rod degeneration)
- Loss of visual field (rod degeneration)

Late Childhood

Severe disease

- Loss of central vision (cone degeneration)

Late Adulthood
Disease progression and endpoints

- **Disease Progression with Patient Age**
  - Hearing impairment
  - Night blindness (start rod degeneration)
  - Loss of visual field (rod degeneration)
  - Loss of central vision (cone degeneration)
  - Complete blindness (rods and cones degenerated)

- **Visual field in degrees vision**
  - 100°
  - 20°
  - 10°
  - 0°

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

Ranges are illustrative, not exact.
Visual fields: Quantifying visual field defects

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

Microperimetry (MAIA)
Automated perimetry (Octopus)
Dark-adapted chromatic (DAC) perimetry (Medmont)
Functional Test of the Light Sensitivity of the Retina

Full Field Stimulus Threshold Test (FST)

• Performed in all subjects in the STELLAR Trial
• Test of most sensitive part of the retina

Goal
Directional improvement in treatment group
Indicator of increased light sensitivity
Imaging of the Structure of the Retina

Marker of Progression of Disease

- Imaging of the retina through high resolution Optical coherence tomography (OCT)
- Visualizes anatomy of the central retina
- Degeneration of photoreceptor cells in the macula is visible at <20° visual field (structure is called Ellipsoid Zone, EZ)

Goal:
Slowing of progression of EZ deterioration
Trial design & demographics

Objectives, trial design and baseline characteristics
Key trial goals/objectives

- Establish early safety and tolerability
- Find early signs of efficacy and how long the effect lasts
QR-421a Phase 1/2 trial in Usher & nsRP

Interim Analysis Q1 2020

**COHORT 1:** 50 µg
4 active, 2 sham

**COHORT 2:** 100 µg
4 active, 4 sham

**COHORT 2B:** 100 µg
Homozygous

**COHORT 3:** 200 µg

24 month follow-up
to measure durability of effect and inform dosing interval

3 months
## Trial population baseline characteristics

<table>
<thead>
<tr>
<th>Cohort/ Dose</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>Visual impairment severity</th>
<th>Months of follow-up</th>
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<tbody>
<tr>
<td>50µg (n=4)</td>
<td>3 homozygous 1 heterozygous</td>
<td>2 Usher 2 nsRP</td>
<td>2 mild-moderate 2 severe</td>
<td>6-11</td>
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<tr>
<td>100µg (n=4)</td>
<td>0 homozygous 4 heterozygous</td>
<td>2 Usher 2 nsRP</td>
<td>3 mild-moderate 1 severe</td>
<td>3-4</td>
</tr>
<tr>
<td>Sham (n=6)</td>
<td>1 homozygous 5 heterozygous</td>
<td>2 Usher 4 nsRP</td>
<td>5 mild-moderate 1 severe</td>
<td>3-9</td>
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Interim results

Safety & tolerability, efficacy and next steps
Safety and tolerability

A total of more than 1350 subject-treatment days at time of IA

- No serious ocular or non-ocular Adverse Events.
- No evidence of inflammation.
- No treatment-associated cataracts.
- No cases of cystoid macular edema or retinal thinning.
25% of treated subjects defined as responder

1 of 3 homozygous versus 1 of 5 heterozygous subjects demonstrated benefit in multiple outcome measures v. untreated eye

Pattern of Benefit

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline visual impairment</th>
<th>Genetic background</th>
<th>Dose</th>
<th>Days</th>
<th>OCT EZ area</th>
<th>DAC</th>
<th>FST</th>
<th>BCVA</th>
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</thead>
<tbody>
<tr>
<td>Responder 1</td>
<td>Moderate</td>
<td>Homozygous</td>
<td>50µg</td>
<td>270</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Responder 2</td>
<td>Severe</td>
<td>Heterozygous</td>
<td>100µg</td>
<td>120</td>
<td>✓</td>
<td>✓</td>
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</table>

= Benefit  
= No change

Mild-moderate disease informative
Severe disease informative
Responder 1

Concordant benefit in FST, EZ area and DAC relative to untreated eye (change from baseline)

- Retinal Light Sensitivity (White FST) (CFB, log cd/m² left and dB right)
  - Direction of Improvement

- Retinal Structure (EZ area, CFB in %)
  - Direction of Improvement

- Visual Field (DAC Cyan HoV total V, CFB, dB.steradian)
  - Direction of Improvement

Waning response at later time points informs dosing interval

50µg dose x 1
Responder 2

Concordant improvement in FST, BCVA and DAC relative to untreated eye (change from baseline)

Retinal Light Sensitivity (White FST)
(CFB, log cd/m² left and dB right)

Retinal Structure
(EZ area, CFB in %)

Visual Field
(DAC Cyan HoV total V, CFB, dB.steradian)

100µg dose x 1
Efficacy summary and trial adaptation

• 2 of 8 QR-421a-treated subjects demonstrated treatment benefit
• 0 of 6 sham-treated subjects met the responder definition
• Early evidence of efficacy at the lower two dose levels tested provide further validation of our platform technology
• Early responder data provide guidance for adaptation of the trial, including
  • Enrichment for homozygous exon 13 mutation subjects in the 100µg dose
  • Dose escalation to a 200µg dose cohort
Progress against trial goals

√ Establish early safety and tolerability
√ Characterize early examples of functional target engagement and if present, duration of benefit to inform dosing interval

√ Assess utility of various outcome measures in moderate versus advanced disease
√ Inform further dose-ranging and the subject enrichment strategy for next steps in development

☐ Characterize the contributions of drug dose and gene dose
☐ Follow treatment-responsive subjects to characterize the duration of response and estimate the dosing interval
IT'S IN OUR RNA