THE ROLE OF RNA THERAPIES IN USHER SYNDROME

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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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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)

2012	2013 - 2016	2017 - 2019	2020
• **Founding of ProQR** • **Initial Focus** on rare lung disease (**Cystic fibrosis**)	• **Shift to Focus on Eye Diseases** • **Development Partnerships** with Academia on rare genetic eye disease (LCA, RP) • **Extensive Preclinical** Development	• **Start of First Clinical Trial: Sepofarsen in LCA10** • Expansion of Clinical Programs to RP with Ush2a mutations and RP due to Rho mutations	• **Clinical programs advancing with lead program in registration trial** • **Molecules** in pre-clinical phase **for >25 additional mutations** causing IRDs

LCA = Leber congenital amaurosis, RP = Retinitis pigmentosa

ProQR inherited blindness platform

UNIQUE PLATFORM FOR PRECISION MEDICINE

Targeted RNA oligo-nucleotide therapies

Intravitreal delivery is routine procedure in ophthalmology

Broad distribution allows for targeting of central and peripheral diseases

Predictive optic cup model

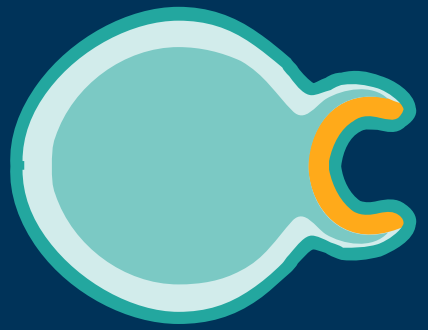
Validating the ProQR inherited retinal disease platform

Predictive retinal organoid model

RNA therapy platform for IRD

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

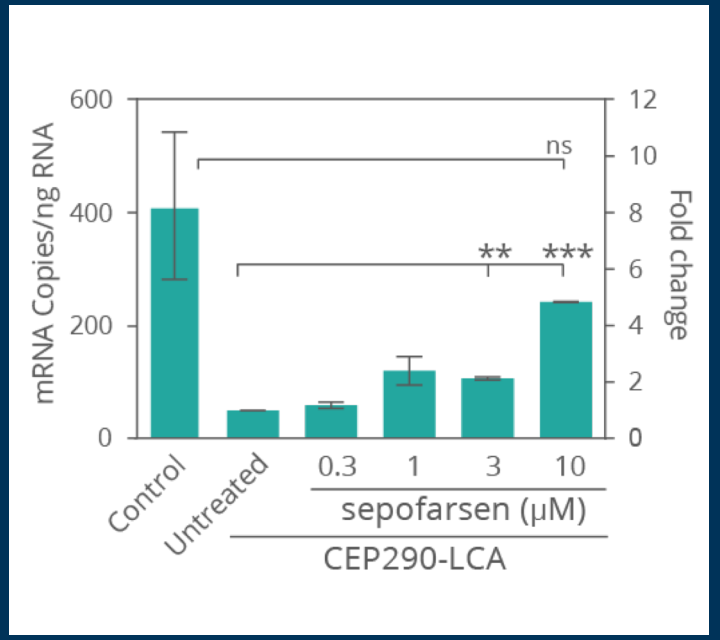
Human retinal organoid model



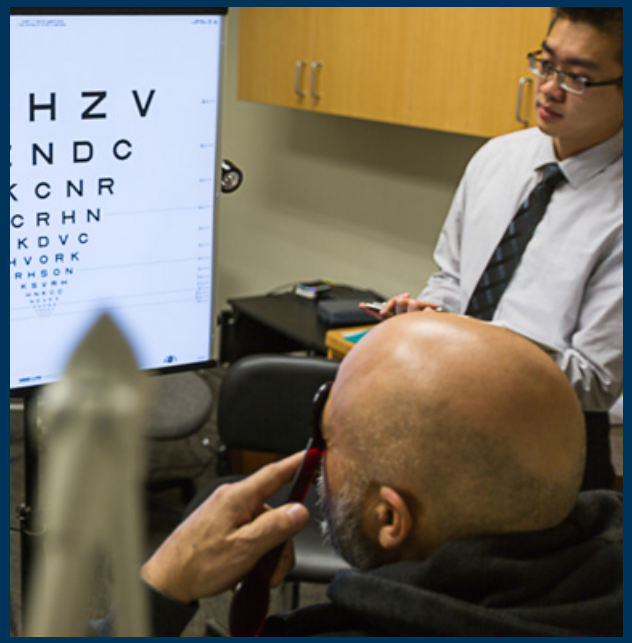
ProQR's Skin to Eye Initiative

Models are generated from small skin punch biopsies from patients with eye diseases

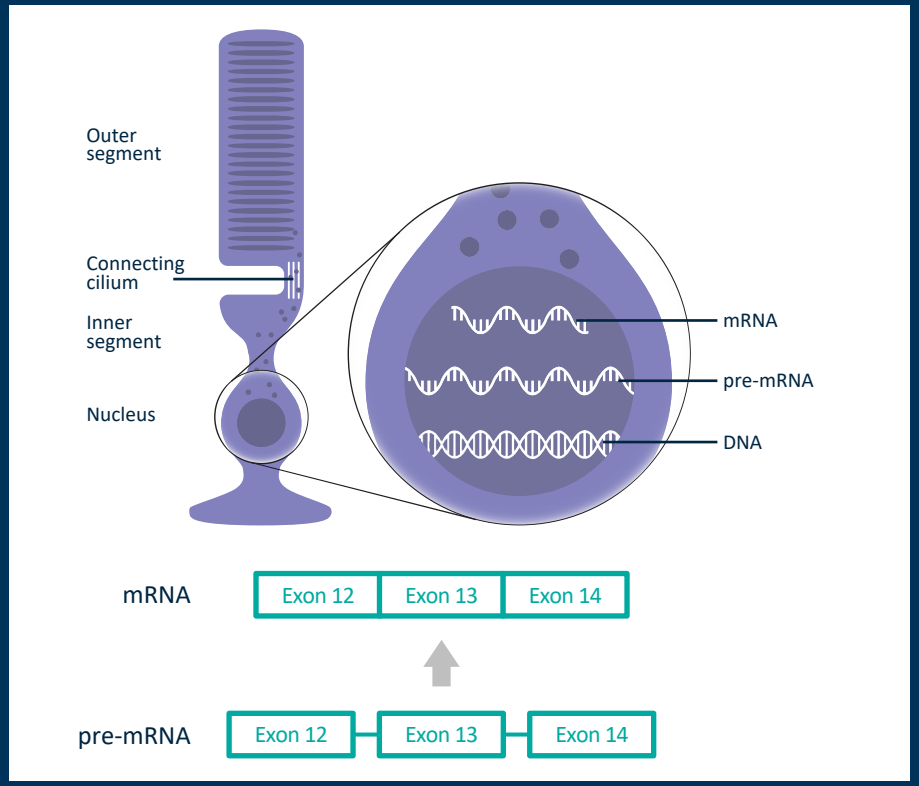
Response in retinal organoids



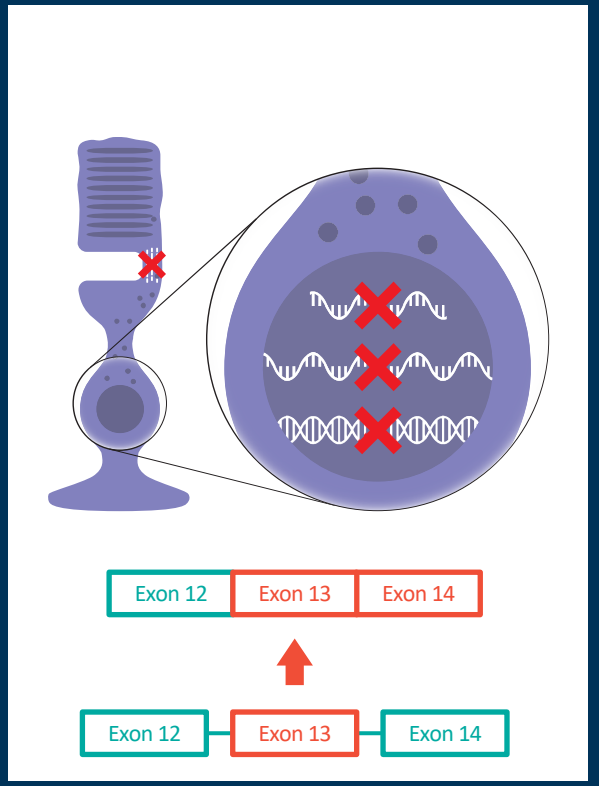
Phase 1/2 human trial



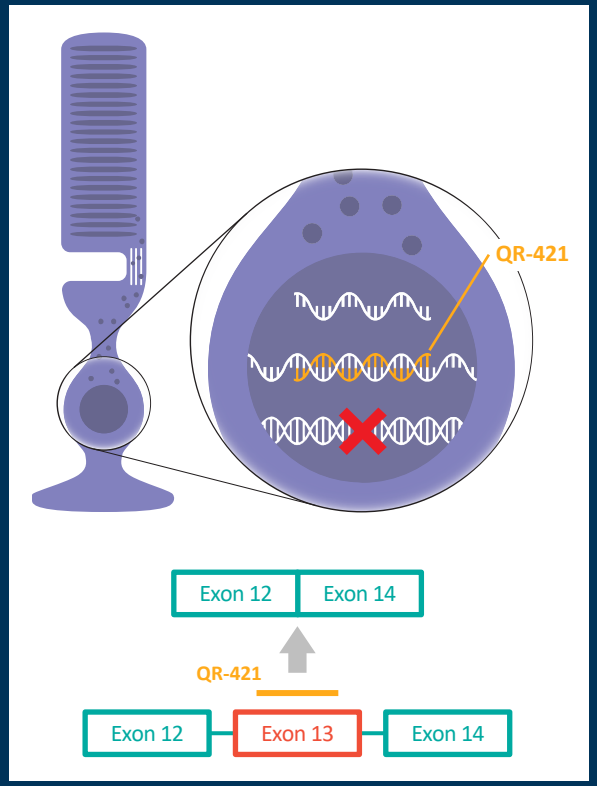
How QR-421a works: exon skipping to remove mutation



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

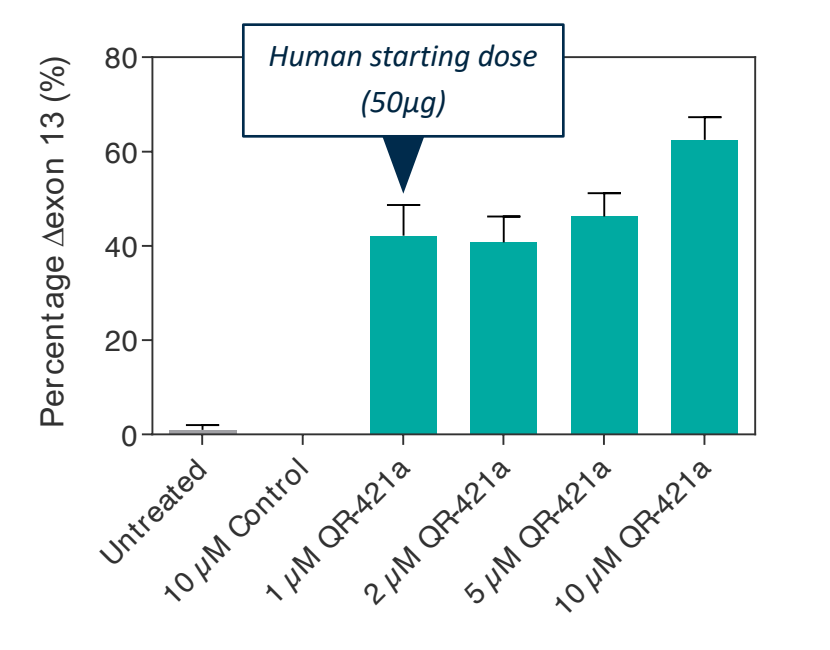


Exclusion of the exon harboring the mutation leads to restoration of functionality of usherin

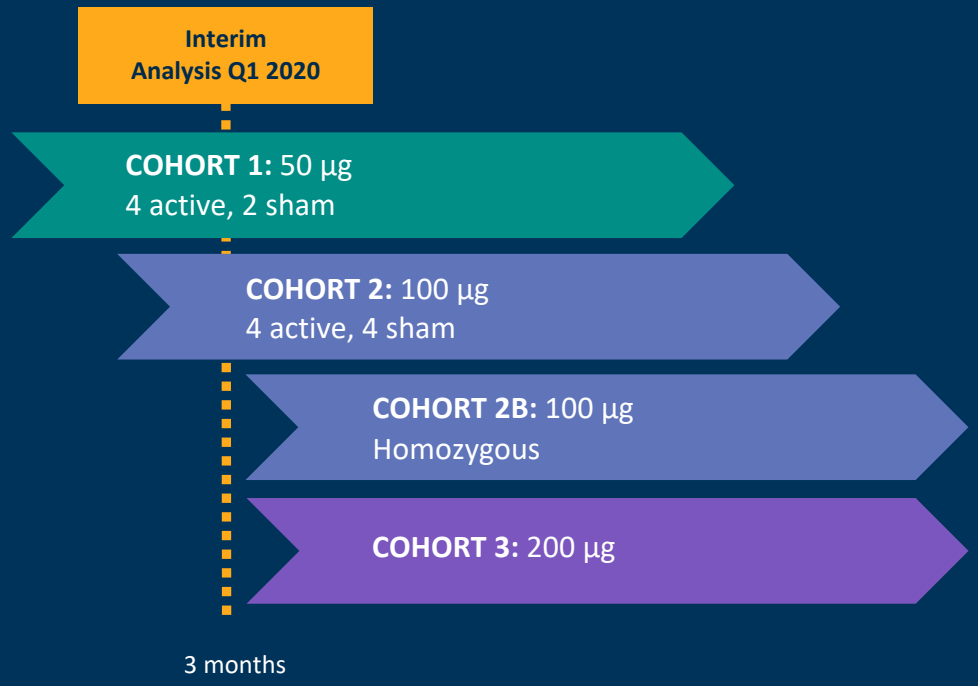
QR-421a RNA therapy in USH2A

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

Response in retinal organoids



Phase 1/2 Stellar trial, (ongoing)



QR-421a RNA therapy

For USH2A mediated Usher syndrome and non-syndromic retinitis pigmentosa

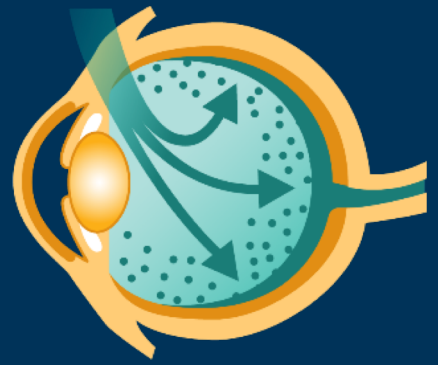
How RNA Therapy is administered

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 | **Severe disease**

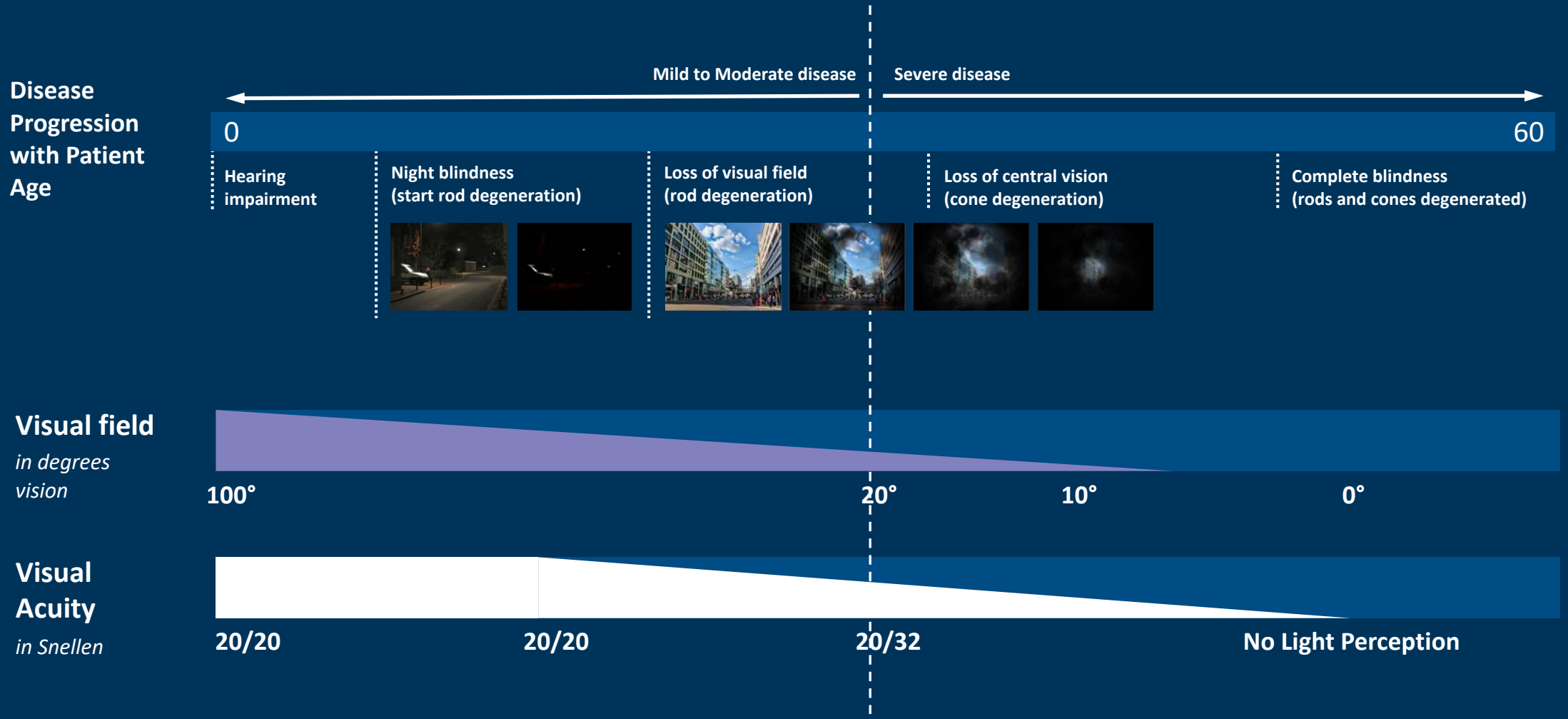
Night blindness (start rod degeneration)

Loss of visual field (rod degeneration)

Loss of central vision (cone degeneration)

Childhood — **Late Adulthood**

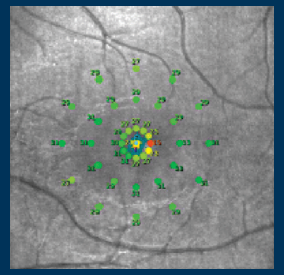
Disease progression and endpoints



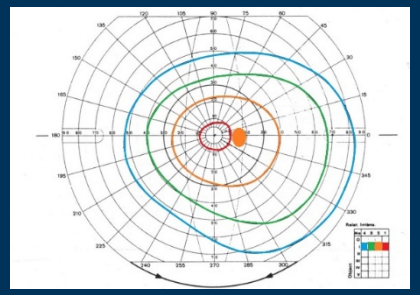
Ranges are illustrative, not exact

Visual fields:

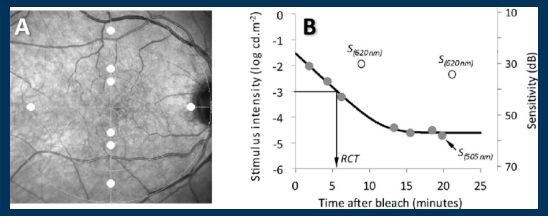
Quantifying visual field defects



Microperimetry (MAIA)

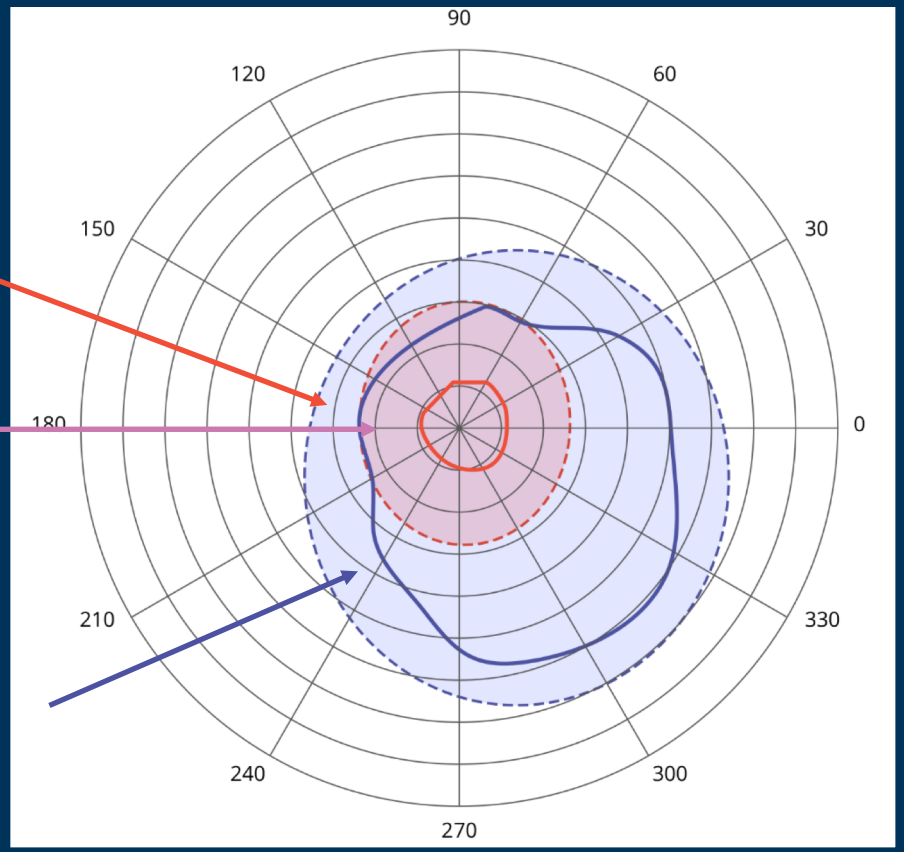


Automated perimetry (Octopus)



Dark-adapted chromatic (DAC) perimetry (Medmont)

Usher syndrome



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

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

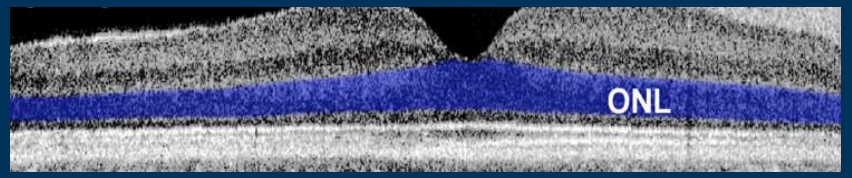
Imaging of the Structure of the Retina

Marker of Progression of Disease

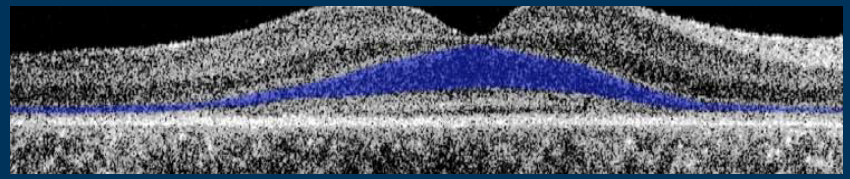
- Imaging of the retina through high resolution Optical coherence tomography (OCT)
  - Visualizes anatomy of the central retina
  - Degeneration of photoreceptor cells in the macula is visible at <20° visual field (structure is called Ellipsoid Zone, EZ)

Goal:
Slowing of progression of EZ deterioration

Normal OCT



Severe Usher Syndrome



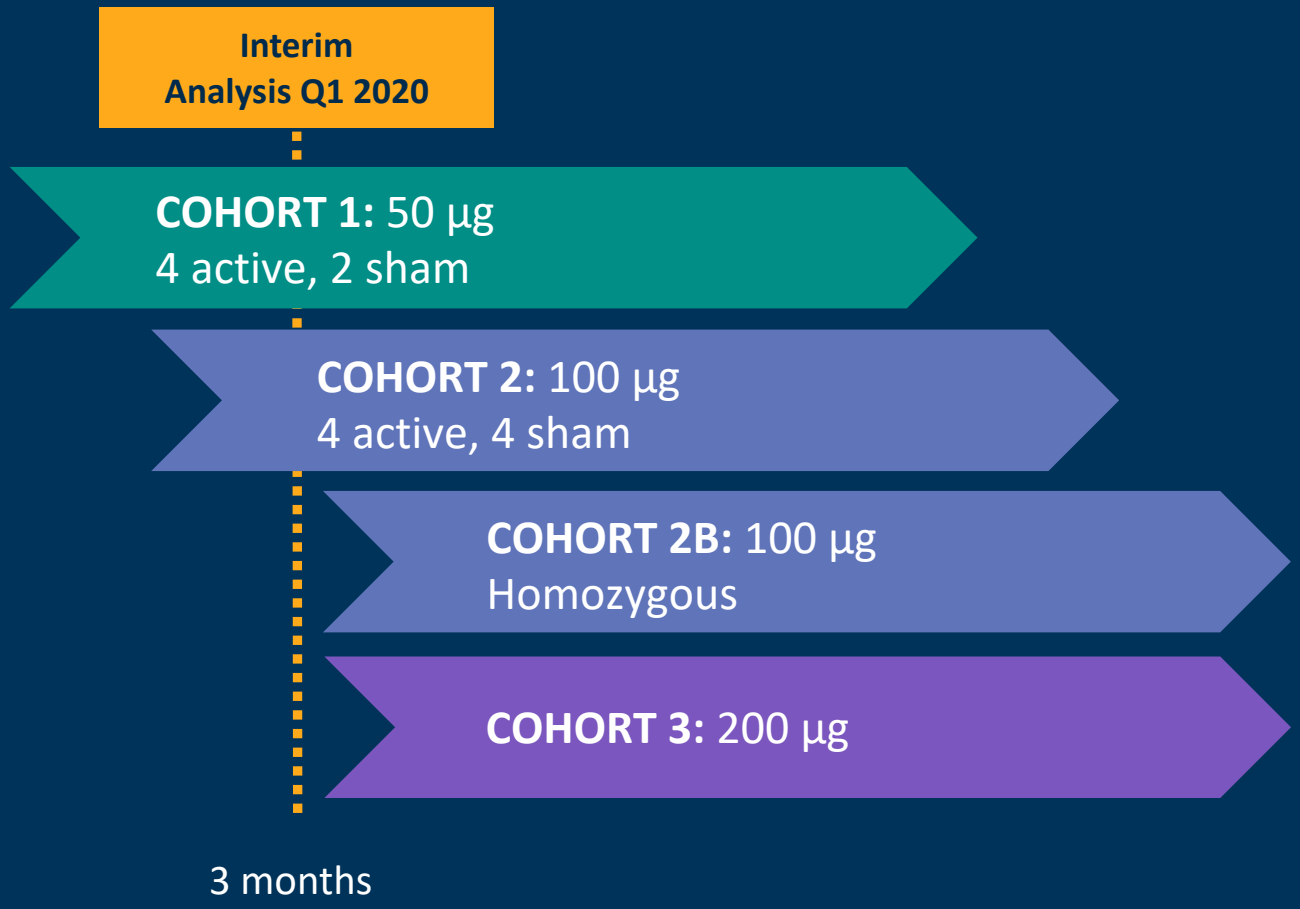
Trial design & demographics

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



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

STELLAR

Trial population baseline characteristics

Cohort/ Dose	Genotype	Phenotype	Visual impairment severity	Months of follow-up
50µg (n=4)	3 homozygous 1 heterozygous	2 Usher 2 nsRP	2 mild-moderate 2 severe	6-11
100µg (n=4)	0 homozygous 4 heterozygous	2 Usher 2 nsRP	3 mild-moderate 1 severe	3-4
Sham (n=6)	1 homozygous 5 heterozygous	2 Usher 4 nsRP	5 mild-moderate 1 severe	3-9

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

Subject	Baseline visual impairment	Genetic background	Dose	Days	OCT EZ area	DAC	FST	BCVA
Responder 1	Moderate	Homozygous	50µg	270	✔	✔	✔	
Responder 2	Severe	Heterozygous	100µg	120		✔	✔	✔

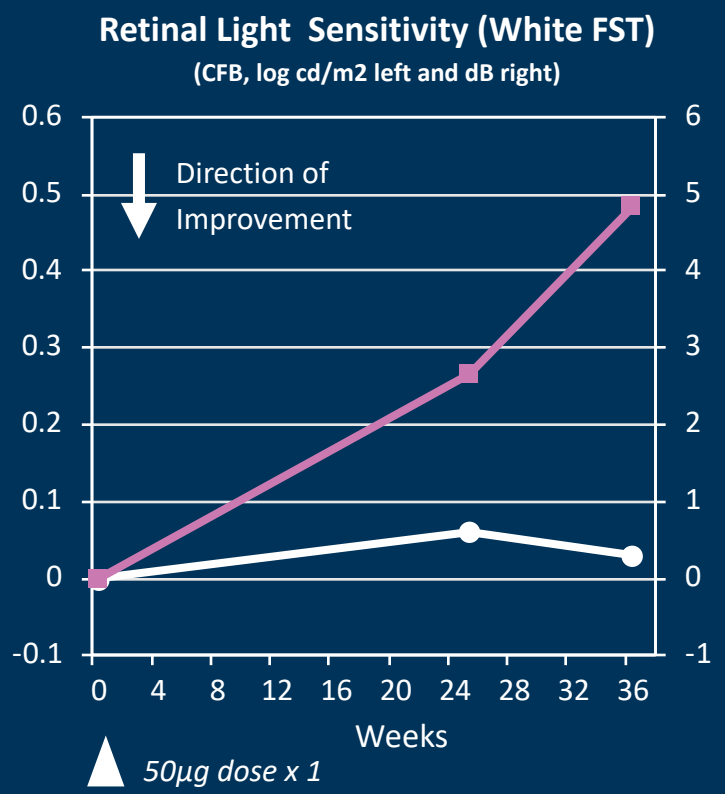
Mild-moderate disease informative

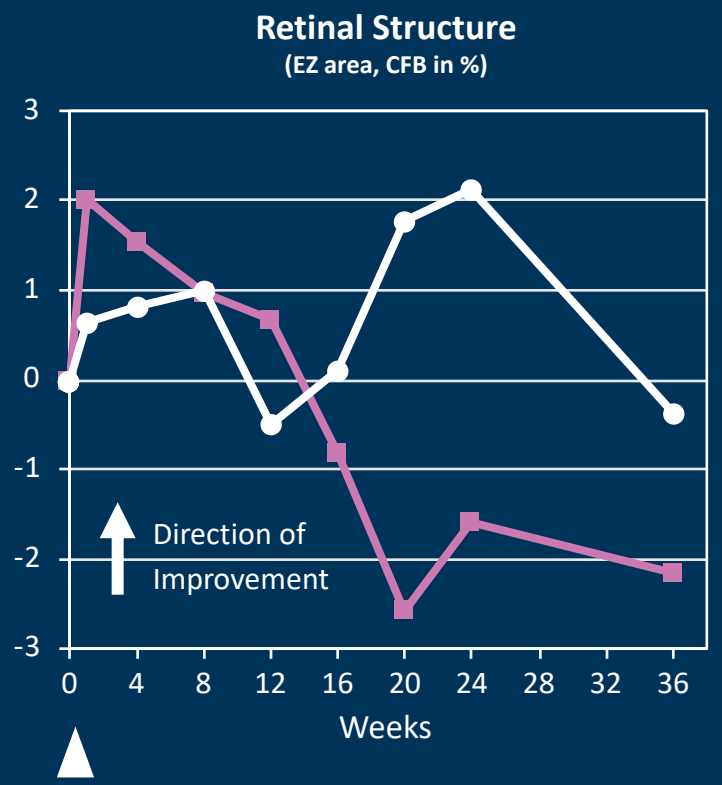
Severe disease informative

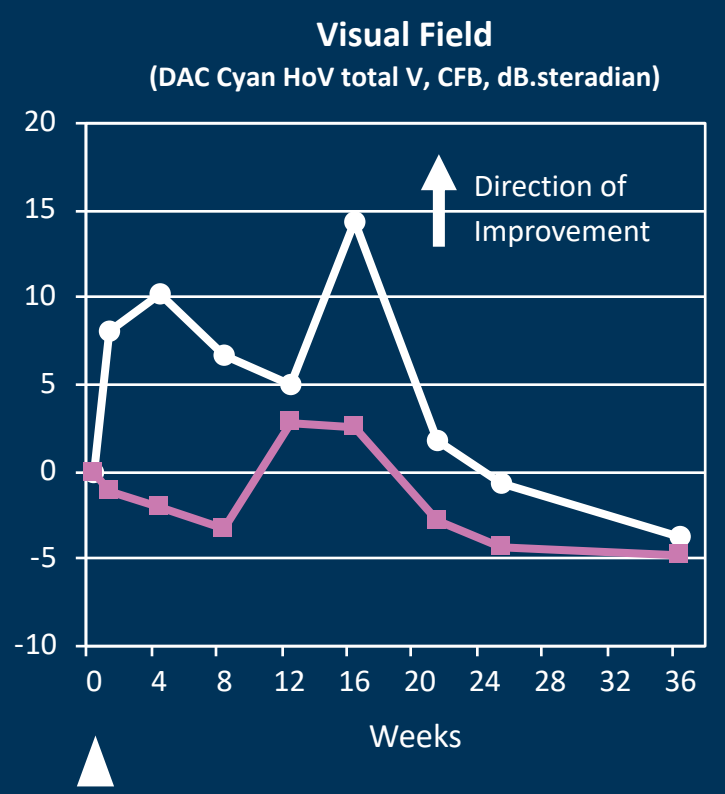
✔ = Benefit ☐ = No change

Responder 1

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





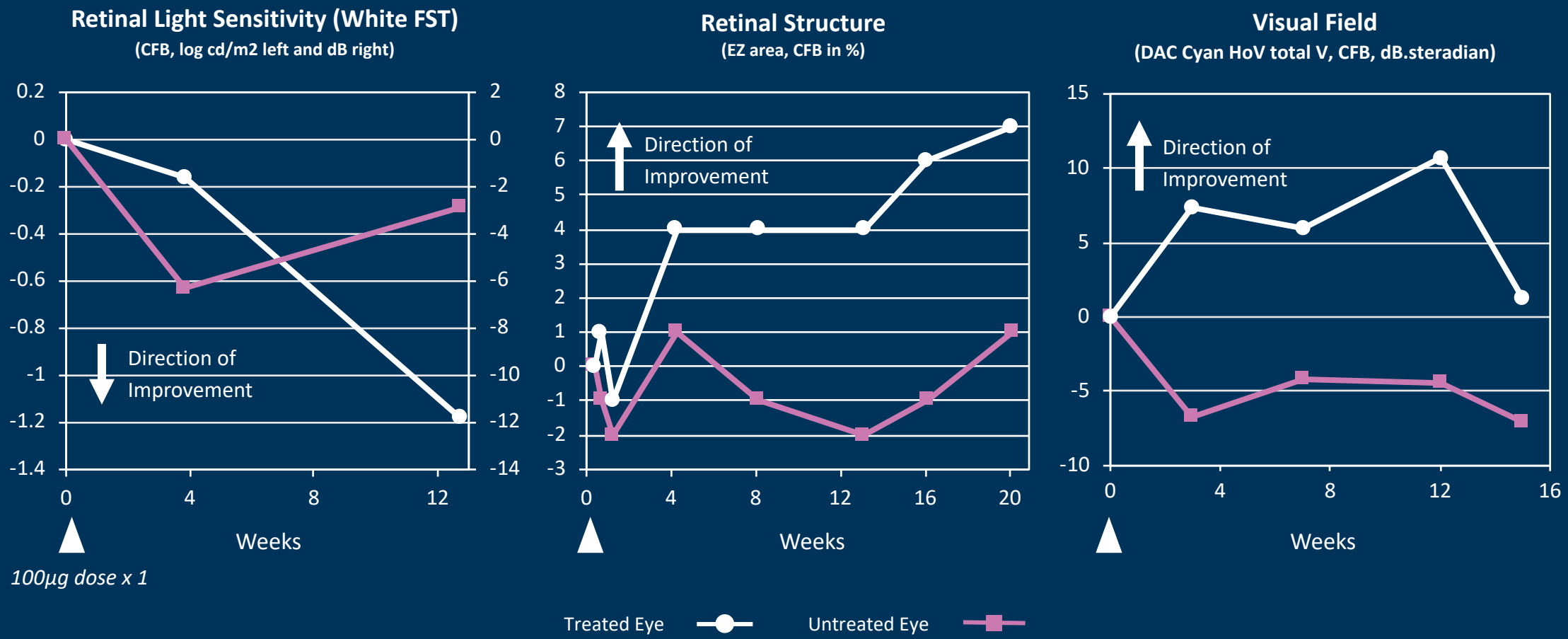


Waning response at later time points informs dosing interval

Treated Eye — Untreated Eye

Responder 2

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



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

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- √ 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

ProQR®

IT'S IN
OUR RNA