PROQR ANALYST EVENT

November 18, 2021

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, regulatory pathway and design of preclinical and clinical trials, research and development, the potential of our technologies and platforms, including Axiomer® and Trident®, statements about our intellectual property rights, future financial position and cash runway, 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 are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. 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 and uncertainties include, among others, the cost, timing and results of preclinical studies and clinical trials and other development activities by us and our collaborative partners whose operations and activities may be slowed or halted by the COVID-19 pandemic; the likelihood of our clinical programs being executed on timelines provided and reliance on our contract research organizations and predictability of timely enrollment of subjects and patients to advance our clinical trials and maintain their own operations; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the potential for future data to alter initial and preliminary results of early-stage clinical trials; the unpredictability of the duration and results of the regulatory review of applications or clearances that are necessary to initiate and continue to advance and progress our clinical programs; feedback and interactions with regulatory authorities with respect to the design of our planned preclinical and clinical activities; the ability to secure, maintain and realize the intended benefits of collaborations with partners; the possible impairment of, inability to obtain, and costs to obtain intellectual property rights; possible safety or efficacy concerns that could emerge as new data are generated in research and development; and general business, operational, financial and accounting risks, and risks related to litigation and disputes with third parties. 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

12:00 – 12:05pm	**Welcome** **Sarah Kiely** *Vice President Investor Relations and Corporate Communications*	
12:05 – 12:15pm	**ProQR's Vision and Strategy** **Daniel A. de Boer** *Founder & CEO*	
12:15 – 12:55pm **12:55 – 1:15pm**	**Sepofarsen** **QR-421a, QR-1123, QR-504a** **Aniz Girach, MD** *Chief Medical Officer*	
1:15 – 1:35pm	**RNA Toolbox** **Gerard Platenburg** *Chief Innovation Officer*	
1:35 – 1:55pm	**Q&A** *moderated by* **Smital Shah** *Chief Business and Financial Officer*	
1:55 – 2:00pm	**Conclusion** **Daniel A. de Boer** *Founder & CEO*	

ProQR®

ProQR's vision is to become a biotech company that creates and provides multiple **life-changing medicines** to help create a world where millions of people living with rare genetic eye diseases **no longer have to experience vision loss**.

Two strategic pillars underpin our approach

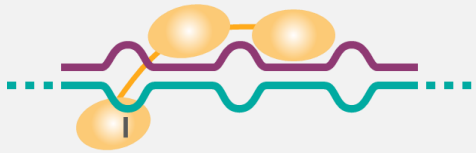
Operating at the intersection of RNA therapy and genetic eye diseases

Genetic eye diseases

RNA editing technologies

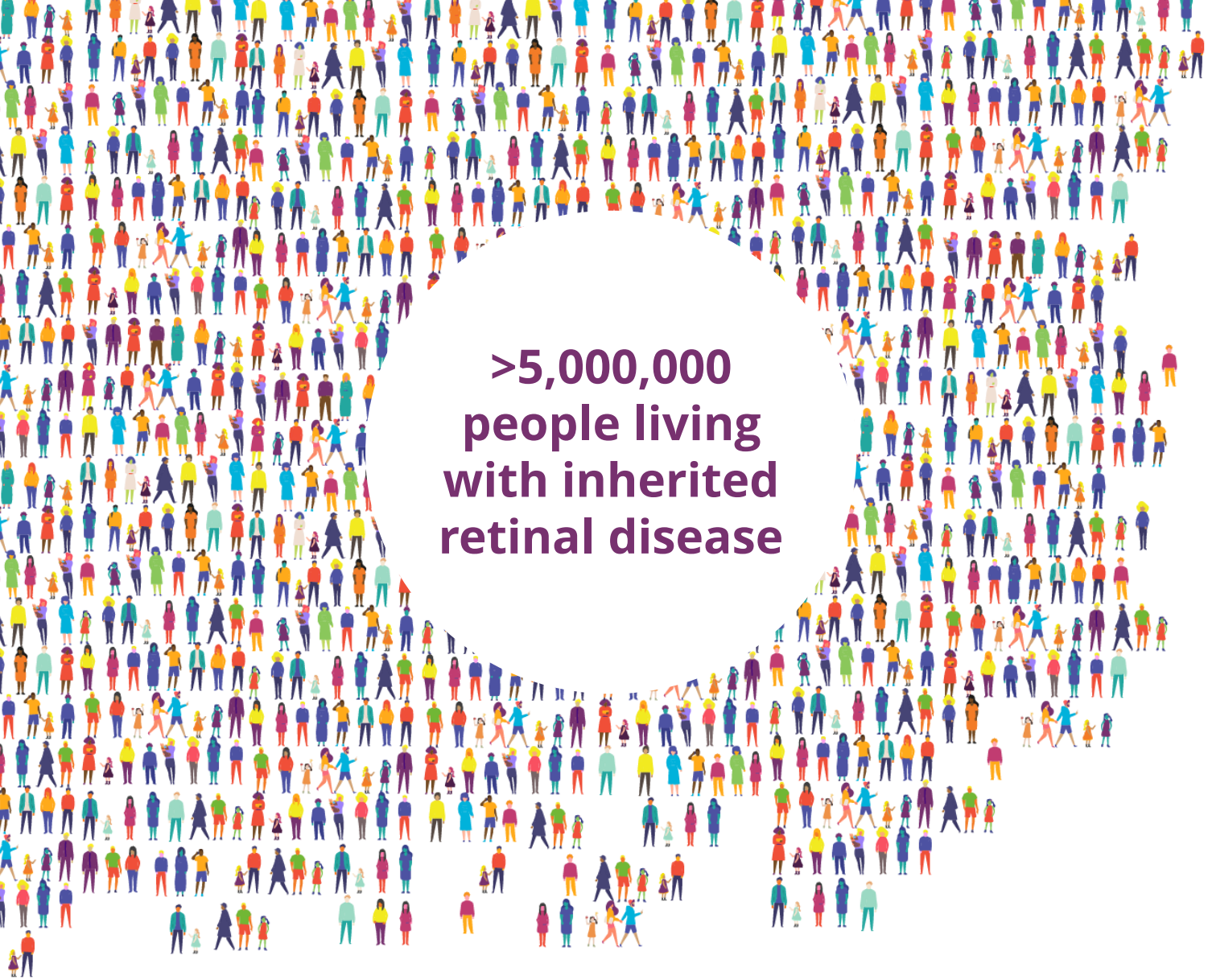
Axiomer®

A-to-I editing



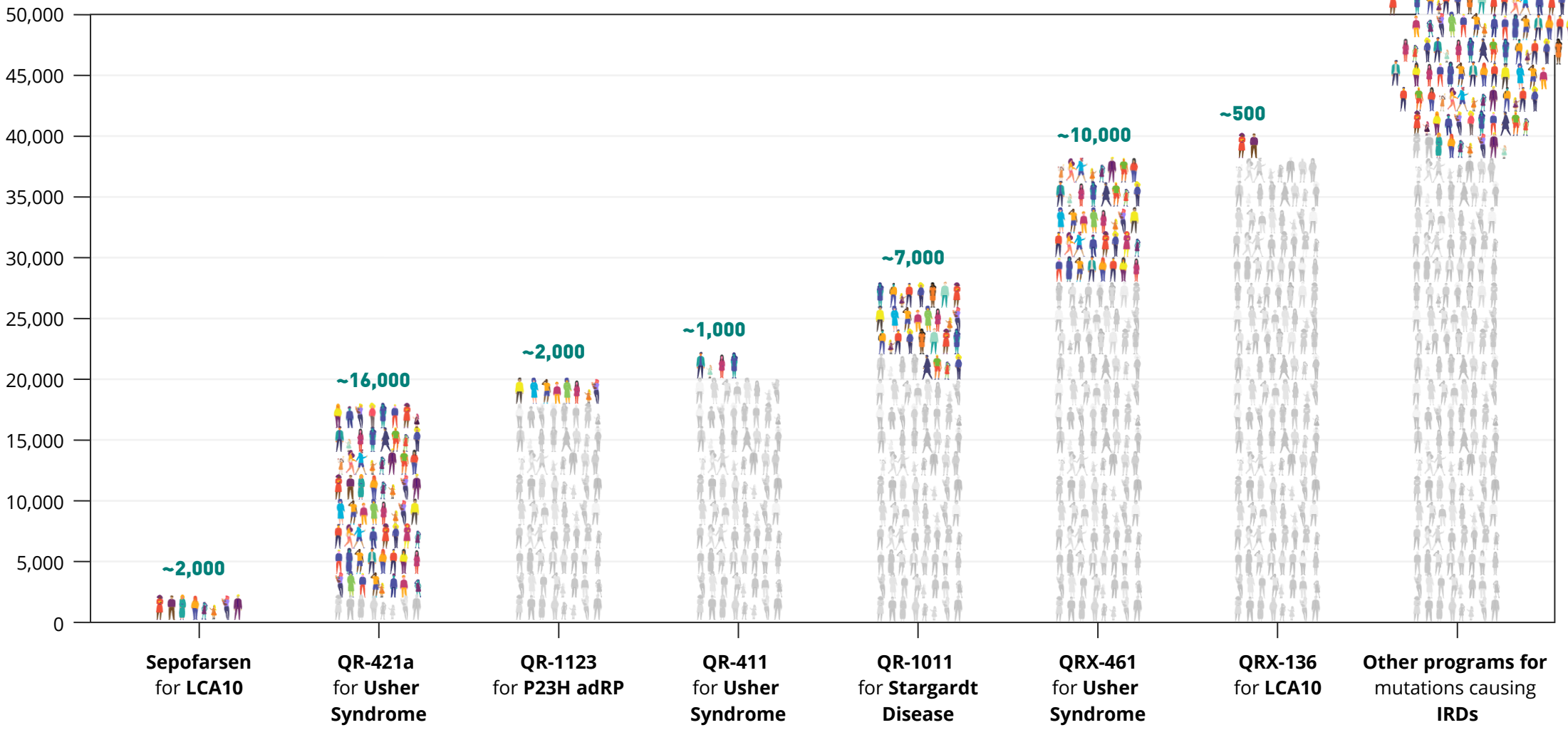
Trident®

U-to-Ψ editing

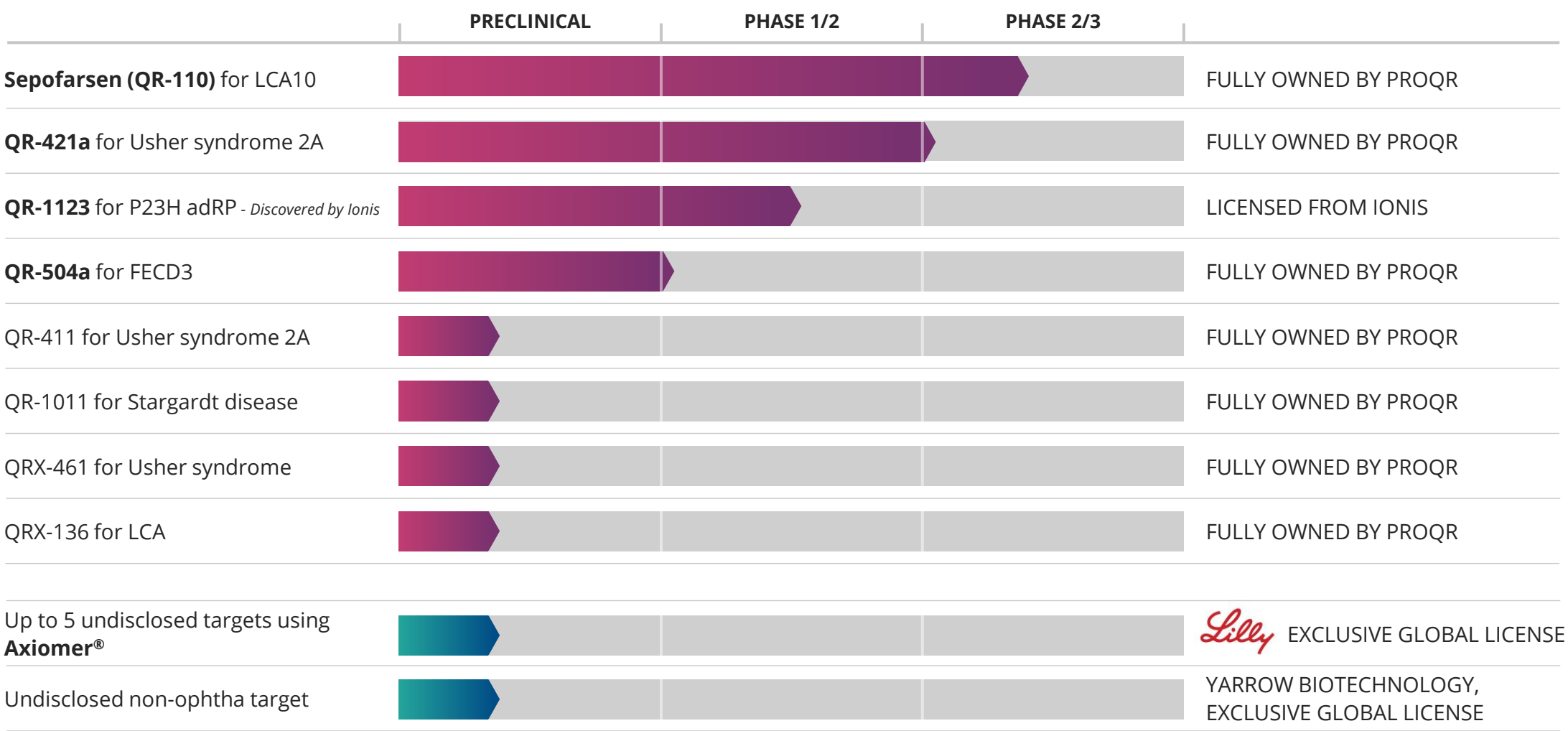


Very few have a treatment

RNA therapies in pipeline for >100,000 IRD patients



ProQR pipeline



Aniz Girach, MD

Chief Medical Officer

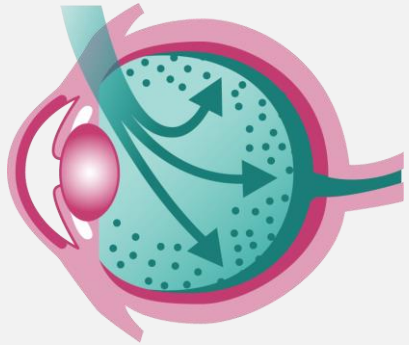
- **Chief Medical Officer at Nightstar Therapeutics** Overseeing development of gene therapies for IRD (most recently)
- **Academia and industry experience** at Eli Lilly, Merck, Alcon and ThromboGenics (Oxurion)
- **Development and approval of Ocriplasmin (Jetrea) a first in class biologic therapy for retinal disease** as well as 3 other drug approvals
- **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
- **Editor of 4 books and author** of over 100 scientific abstracts and manuscripts

Ocular RNA therapy

The eye is exquisitely suited to ProQR's RNA antisense oligonucleotide approach

Ocular Therapy

- Eye is a small and enclosed organ
  - Cleaner safety profile
- Deliver directly into the target organ
- Effects of drugs are easily visible
- Eye is a relatively immune-privileged site

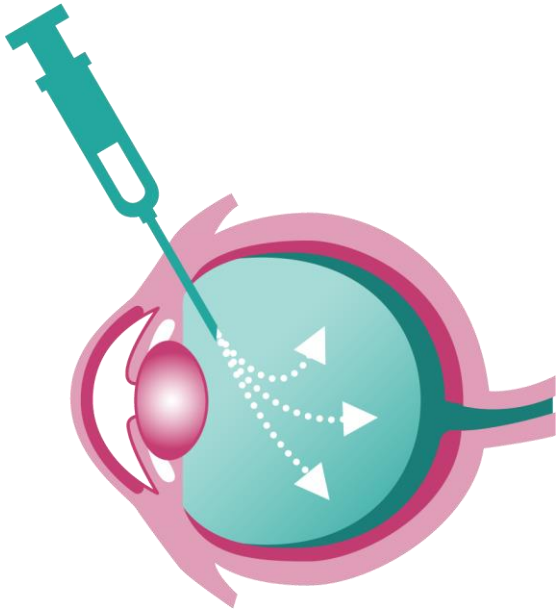


RNA Therapy

- Naked molecules
  - less immunogenicity/inflammation
  - Not limited to small transgene-based diseases
- Delivered via intravitreal (IVT) injection
  - In-office procedure
  - Fewer complications
- Access to the entire retina
  - Can treat diseases at an earlier stage

IVT administration is a routine procedure

Intravitreal administration

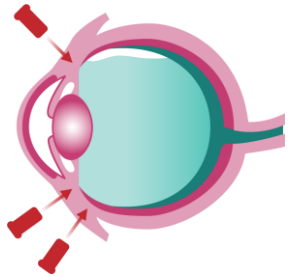


Routine procedure

- Allows wide patient accessibility
- Infrequent dosing
- Naked delivery

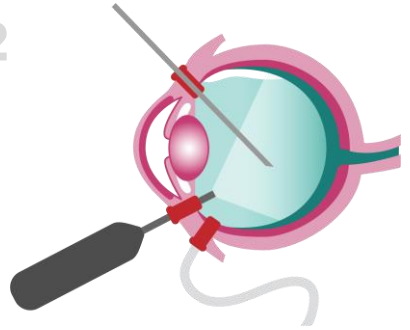
Sub-retinal surgery

1



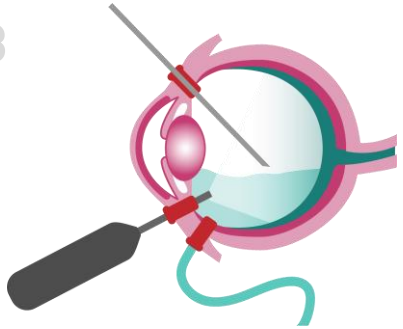
3 ports are generated in the wall of the eye to allow access for tools

2



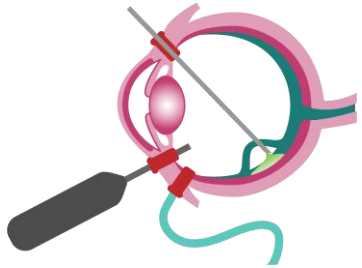
A light and a needle are inserted into the eye to locate the place of injection

3



Vitrectomy: The vitreous gel is cut/sucked out of the eye to aid visualization and ease of injection

4

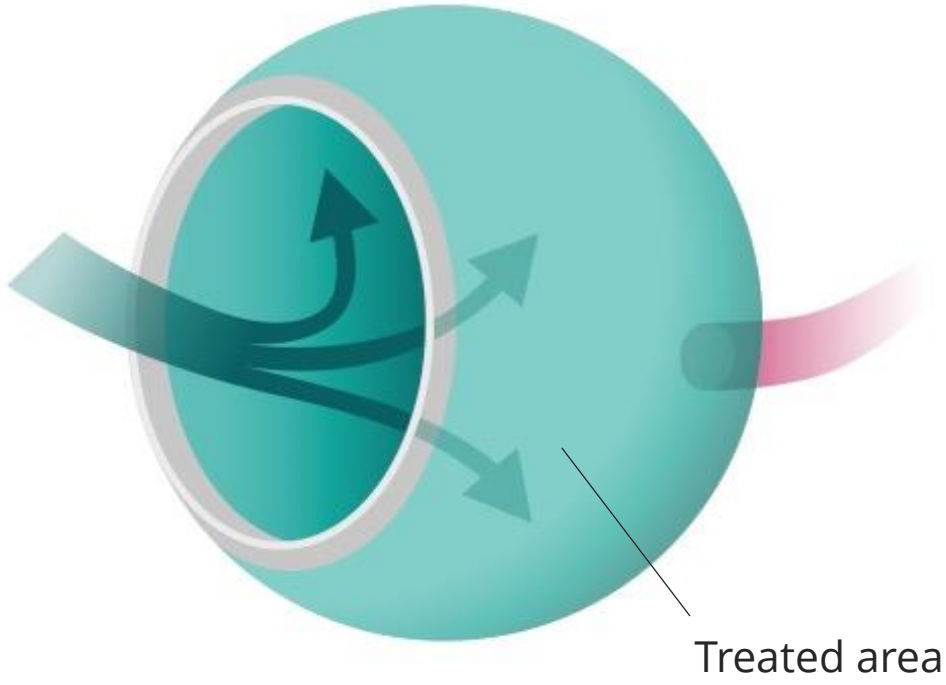


The needle enters the retina, lifting off the retina until a bleb is formed, then depositing drug in the sub-retinal space

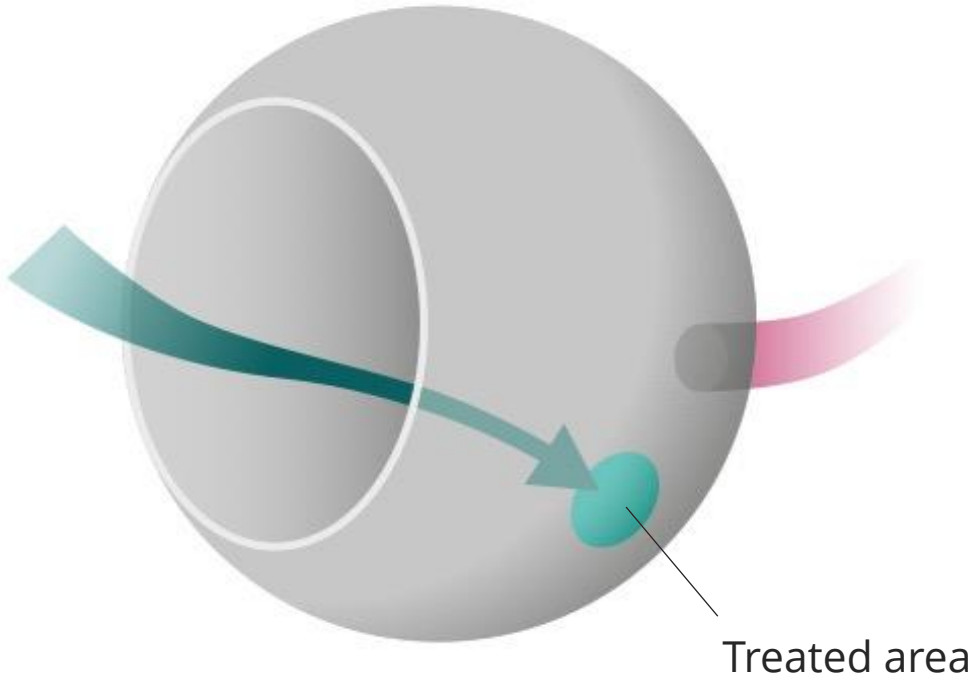
RNA IVT therapy enables broad distribution

Targets central and peripheral diseases

Intravitreal administration can target entire retina



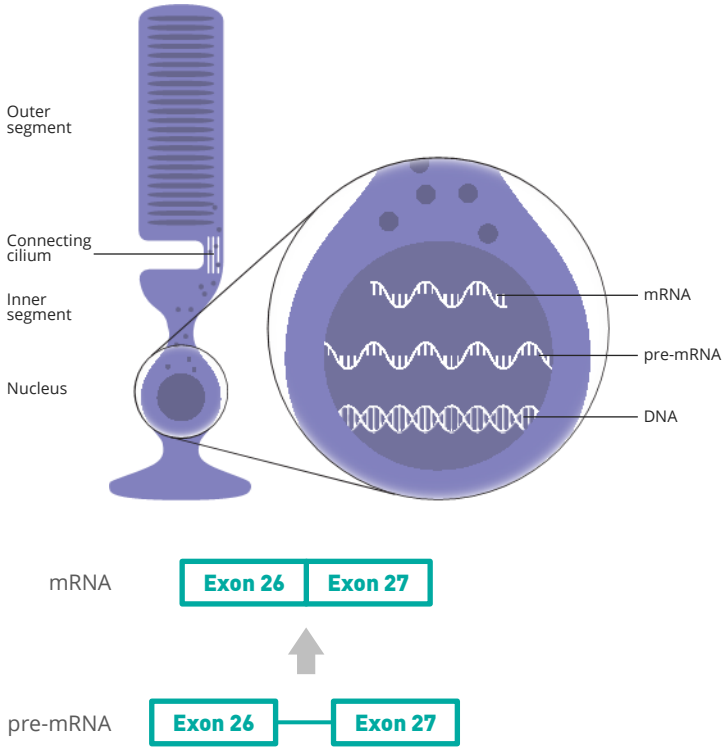
Sub-retinal procedure treats mainly central [6] mm of retina



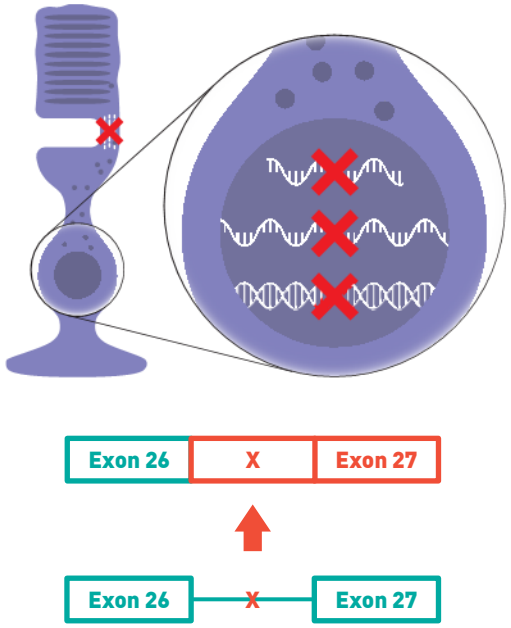
Sepofarsen for Leber congenital amaurosis 10

Sepofarsen for LCA10

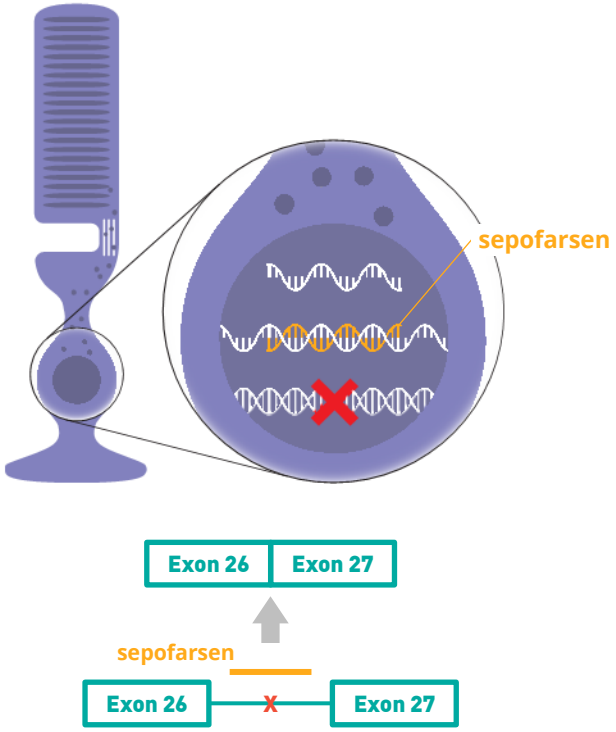
Splice correction for c.2991+1655A>G CEP290 mRNA



In wild-type cells *CEP290* maintains cilium structure and enables normal protein transport



In c.2991+1655A>G-LCA10 cells protein transport is hampered and the outer segment degenerates



Exclusion of the cryptic exon from the mutated mRNA leads to wild-type Cep290 protein

Sepofarsen (QR-110) for *CEP290*-mediated LCA10

LCA10

Lose sight in first years of life

No approved therapy currently available

c.2991+1655A>G mutation (p.Cys998X) affects **~2,000** patients in the Western world

RNA therapy: 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

- Top-line Phase 1/2 clinical trial results showed rapid, significant and durable activity and was well tolerated
- Orphan drug designation & Rare pediatric disease designation
- FDA Fast track designation and access to EMA PRIME program
- Ph 2/3 *Illuminate* trial completed enrollment January 2021; top-line data expected late Q1/early Q2 2022
- Pediatric trial underway

Sepofarsen clinical trials for LCA10

	Trial phase	Trial objectives
	Phase 1/2 (completed)	Safety & tolerability
inSight	Phase 1/2 extension (ongoing)	Continued treatment for Phase 1/2 patients, 2nd eye treatment
	Mobility (ongoing)	Validate the mobility course as an endpoint in clinical trials
Brighten	Pediatric (ongoing)	Safety and tolerability in children < 8 yrs age
Illuminate	Phase 2/3 (ongoing)	Potential pivotal trial in ≥8 yrs age

Sepofarsen clinical trials for LCA10

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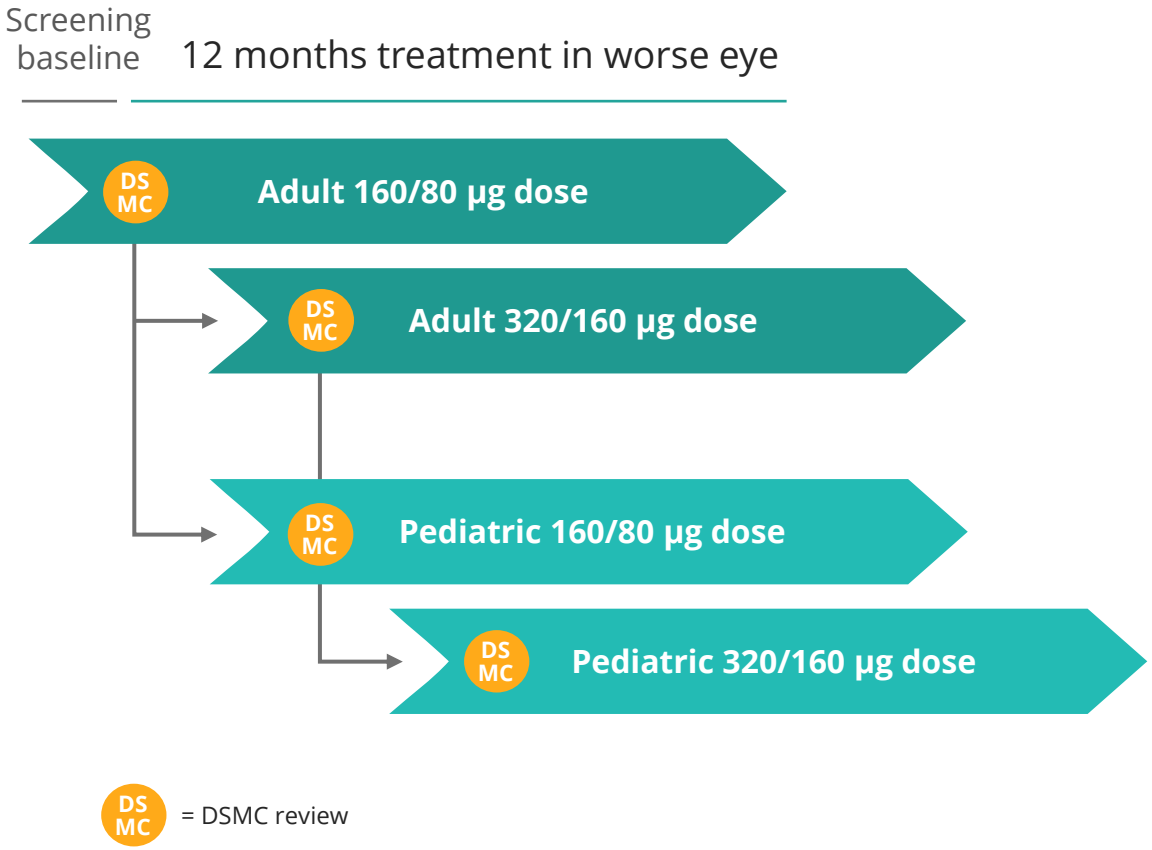
Sepofarsen Phase 1/2 trial design

LCA10 patients with 1 or 2 copies of c.2991+1655A>G mutation

Phase 1/2 Study



Design

- Open-label, Multiple Dose, Dose Escalation Phase 1/2 Study
- Treatment in one eye, the untreated eye is the control

Inclusion

- Enrolled 11 adults and children with LCA10 due to the c.2991+1655A>G mutation in the *CEP290* gene

Endpoints

- Primary endpoint: safety & tolerability
- Secondary endpoints: best corrected visual acuity (BCVA), full field stimulus test (FST) and mobility course

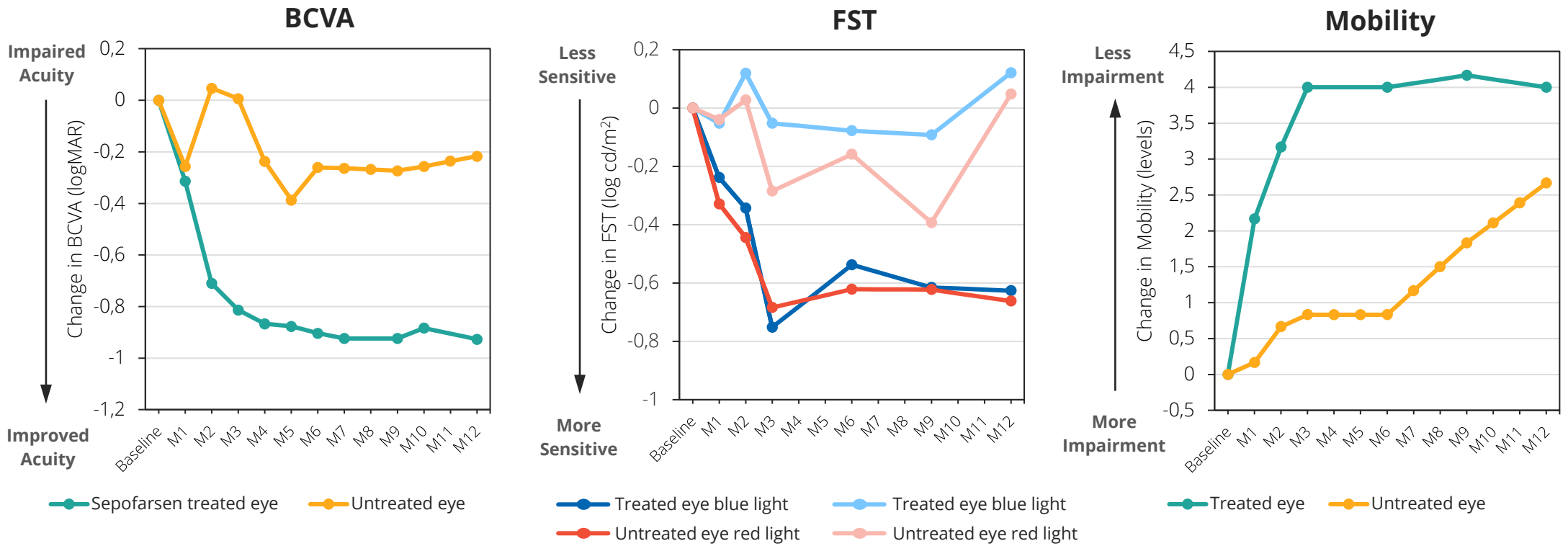
Phase 1/2 study safety summary

Positive benefit/risk in 160/80 µg cohort with 50% incidence of lens opacity; Subclinical retinal findings in 320/160 µg cohort

	Cataracts	Cystoid Macular Edema	Retinal thinning
SAE/AE	6 SAE (surgery)/2 AE	0 SAE / 2 AE	0 SAE / 2 AE
Dose-dependent incidence	Yes	Yes	Yes
Timing (160/80 µg cohort)	8-12 months	No cases	No cases
Timing (320/160 µg cohort)	3-9 months	3-4 months	3-10 months
Treatment-responsive	Yes	Yes	Stabilized

Ph1/2 key outcomes in target registration dose

Onset of effect within 3 months, sustained out to month 12 in the 160/80 µg dose group (n=6)



Eye	BCVA – logMAR (n=6)	Red FST – log cd/m2 (n=6)	Blue FST – log cd/m2 (n=6)	Mobility course – composite score (n=6)
Treated	**-0.93 (0.43) p=0.13 vs. CE**	**-0.66 (0.14) p<0.05 vs. CE**	**-0.63 (0.31) p=0.09 vs. CE**	**4.0 (1.27) p=0.06 vs. CE**
Untreated	-0.22 (0.11)	0.05 (0.17)	0.12 (0.16)	2.7 (1.11)

Phase 1b/2 sepofarsen trial – PQ-110-001; NCT03140969

Sepofarsen clinical trials for LCA10

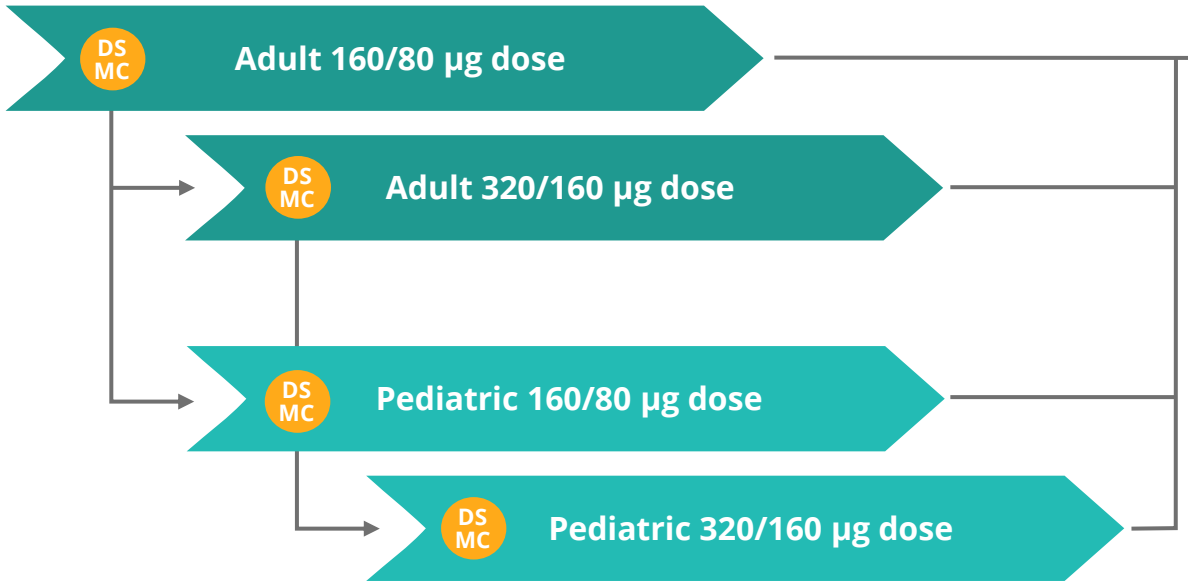
	Trial phase	Trial objectives
	Phase 1/2 (completed)	Safety & tolerability
inSight	**Phase 1/2 extension (ongoing)**	**Continued treatment for Phase 1/2 patients, 2nd eye treatment**
	Mobility (ongoing)	Validate the mobility course as an endpoint in clinical trials
Brighten	Pediatric (ongoing)	Safety and tolerability in children < 8 yrs age
Illuminate	Phase 2/3 (ongoing)	Potential pivotal trial in ≥ 8 yrs age

Phase 1/2 + *InSight* extension trial design

Open label, extension trial for Phase 1/2 participants

Phase 1/2 Study

Screening baseline — 12 months treatment in worse eye



InSight extension study enables continued treatment for Phase 1/2 participants

inSight

DS MC = DSMC review

InSight extension study

Responder overview and qualitative impact summary

Participant	Treated eye	Baseline vision	BCVA	FST Blue	FST Red	Mobility
P1	1st Eye	LP	no	√	√	no
	2nd Eye	LP	no	√	√	no
P2	1st Eye	LP	√	√	√	√
	2nd Eye	LP	√	√	√	no
P3	1st Eye	HM	√	√	√	√
	2nd Eye	HM	√	√	√	√
P11	1st Eye	Chart	√*	√	√	√
	2nd Eye	Chart	√*	√	√	√*
P7	1st Eye	Chart	√**	Missing data^	Missing data^	√
	2nd Eye	Chart	no**	Missing data^	Missing data^	no
P5	1st Eye	HM	√	√	√	√
P8	1st Eye	CF	√	√	√	no
P6	1st Eye	LP	no	√	√	no

Legend

√	Response
no	No response
Missing data	Not measured or data not available
LP	Light perception
CF	Counting fingers
HM	Hand motion
Chart	On eye chart
BVCA	Best corrected visual acuity
FST	Full field stimulus test
Mobility	Mobility course

Threshold for response: BCVA >-0.2 logMAR (green) or >-0.3 logMAR (dark green), FST -.0.5 log cd/m2, Mobility 2 light levels

* Started with good vision (0.63 logMAR and moved -0.25 – potential ceiling affect) (2nd eye started with score of 15 in mobility course – potential ceiling affect)

** Started with good vision (1st eye 1.05 logMAR and moved -0.25 – potential ceiling affect; 2nd eye started at 0.7 - latest measurement 0.54 - potential ceiling affect)

^ FST data are missing for participant P7 due to incorrect baseline FST procedure

InSight extension study

Responder overview and qualitative impact summary

Participant	Treated eye	Baseline vision	BCVA	FST Blue	FST Red	Mobility	Qualitative/patient experience
P1	1st Eye	LP	no	√	√	no	Treatment in both eyes, not missed injection in 4 yrs – Significant FST response and convinced treatment is working
	2nd Eye	LP	no	√	√	no	
P2	1st Eye	LP	√	√	√	√	Went from 'light perception' to 'on chart' – Able to read print and make out bus numbers and traffic lights
	2nd Eye	LP	√	√	√	no	
P3	1st Eye	HM	√	√	√	√	Went from 'hand motion' to 'on chart' – able to resume work as a carpenter
	2nd Eye	HM	√	√	√	√	
P11	1st Eye	Chart	√*	√	√	√	Homozygous patient - reported in Nature Medicine, expected to see smaller font and more words
	2nd Eye	Chart	√*	√	√	√*	
P7	1st Eye	Chart	√**	Missing data^	Missing data^	√	Increase in contrast sensitivity – ability to now see the holes in a slice of bread
	2nd Eye	Chart	no**	Missing data^	Missing data^	no	
P5	1st Eye	HM	√	√	√	√	Went from 'hand motion' to 'on chart' - Pediatric
P8	1st Eye	CF	√	√	√	no	Pediatric – able to drive a 4-wheeler on road instead of only on a field
P6	1st Eye	LP	no	√	√	no	

Threshold for response: BCVA >-0.2 logMAR (green) or >-0.3 logMAR (dark green), FST -.0.5 log cd/m2, Mobility 2 light levels

* Started with good vision (0.63 logMAR and moved -0.25 – potential ceiling affect) (2nd eye started with score of 15 in mobility course – potential ceiling affect)

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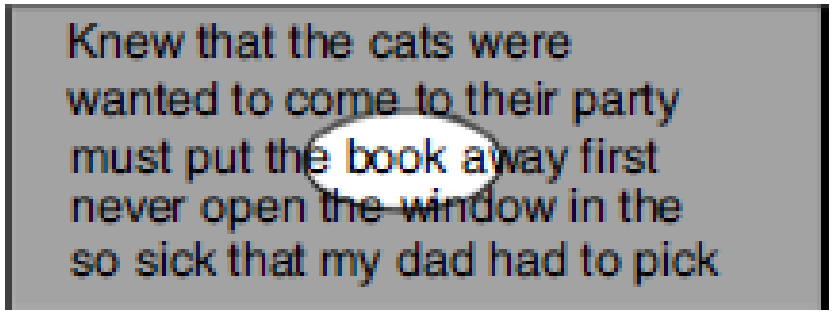
^ FST data are missing for participant P7 due to incorrect baseline FST procedure

Case study P11 – homozygous patient

P11 would be expected to see smaller font and more words compared to baseline

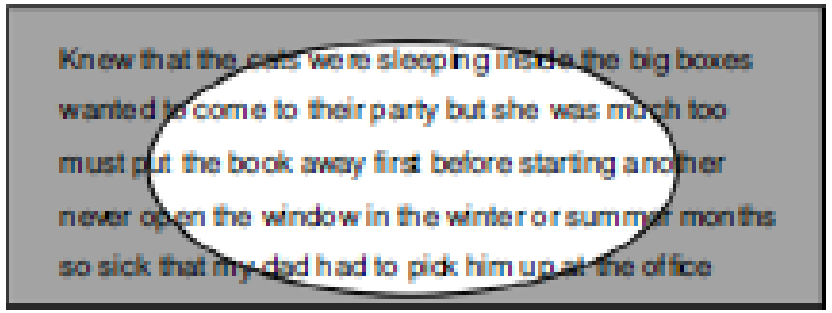
Reading simulation

Before treatment (Baseline)
14 point font, one word



14mm'2◇

After treatment (Month 4)
8 point font, more words



Cideciyan, A.V., Jacobson, S.G., Ho, A.C. et al.
Durable vision improvement after a single treatment with antisense oligonucleotide sepofarsen: a case report.
Nat Med 27, 785–789 (2021).

Case study P2 – from LP to being on chart

Seeing things he hadn't seen in more than 10 years

- **Went from "LP" to "on chart"** in first eye. Untreated eye stayed at LP for 21 months. Second eye was treated on after 21 months with same response
- Called his doctor to say that **he could read signs** at the airport
- As a passenger in the car, started noticing **headlights and streetlights**
- **See the number** on the bus and distinguish between **red and green traffic lights**
- **Read print** for the first time in decades

Case study P3 – from HM to being on eye chart

Able to resume work as a carpenter

Participant P3

- Baseline:
  2.4 logMAR (20/5000)
- 9 months:
  0.58 logMAR (20/63)
- Improvement:
  1.82 logMAR*

* From being worse than legally blind to navigating freely, watching TV and being able to see family faces.

Baseline (2.4 logMAR) | **M3 (1.12 logMAR)** | **M9 (0.58 logMAR)**

Using "Thru My Eyes" App

Sepofarsen clinical trials for LCA10

	Trial phase	Trial objectives
	Phase 1/2 (completed)	Safety & tolerability
inSight	Phase 1/2 extension (ongoing)	Continued treatment for Phase 1/2 patients, 2nd eye treatment
	Mobility (ongoing)	**Validate the mobility course as an endpoint in clinical trials**
Brighten	Pediatric (ongoing)	Safety and tolerability in children < 8 yrs age
Illuminate	Phase 2/3 (ongoing)	Potential pivotal trial in ≥ 8 yrs age

Mobility course clinical trial update

Objective

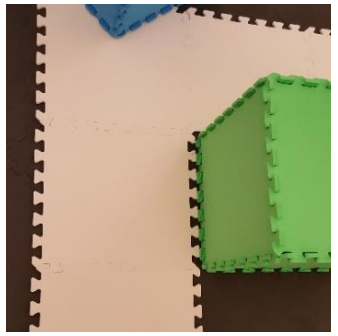
- Study to Evaluate the Feasibility and Variability of Select Vision Assessments in Subjects with a Leber Congenital Amaurosis (LCA) Type Phenotype – validate as an endpoint for clinical trials

Status

- Trial complete: 48 pts included in final analysis with enrollment completed in June 2021
- Performed at 17 sites across 9 countries
- Data analysis underway

Next steps

- Discuss with Regulators



High-Contrast Visual Navigation Challenge
at 1, 4, 10, 50, 125, 250, 400 lux
(Ora, Inc. HCVNC™)

Low-Contrast Visual Navigation Challenge
at 1, 4, 10, 50, 125, 250, 400 lux
(Ora, Inc. LCVNC™)

Sepofarsen clinical trials for LCA10

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	Phase 1/2 (completed)	Safety & tolerability
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Brighten	**Pediatric (ongoing)**	**Safety and tolerability in children < 8 yrs age**
Illuminate	Phase 2/3 (ongoing)	Potential pivotal trial in ≥ 8 yrs age

Brighten pediatric clinical trial update

Primary endpoint safety with secondary endpoints of BCVA and FST

Objective

- Safety and tolerability study in children under 8 years of age with Leber congenital amaurosis 10 (LCA10) due to the c.2991+1655A>G (p.Cys998X) mutation

Design

- Open-label dose escalation, followed by a double-masked randomized part
- 10 sites in up to 7 countries
- Subjects had to have a best-corrected visual acuity (BCVA) equal to or better than Light Perception and equal to or worse than 20/50

Status

- First patient was dosed in the open-label dose escalation part in April 2021; dose escalation phase now completed with 5 participants dosed to date

Next steps

- Randomization phase will include 5 participants on 40 µg and 5 participants on 80 µg, to be dosed every 6 months for 2 years
- Anticipate enrollment to complete by H1 2022

Sepofarsen clinical trials for LCA10

	Trial phase	Trial objectives
	Phase 1/2 (completed)	Safety & tolerability
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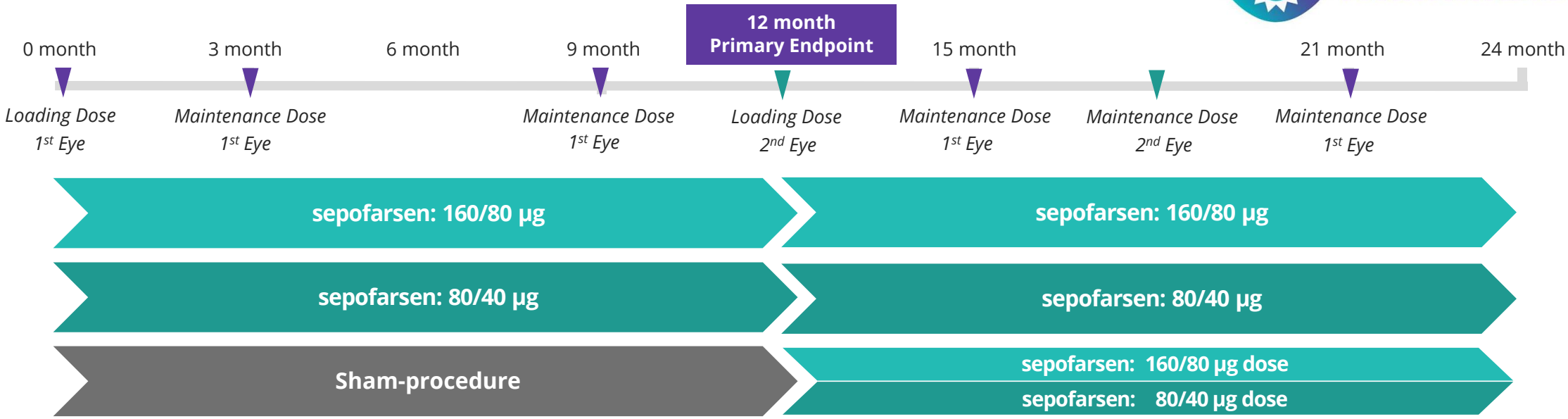
	Mobility (ongoing)	Validate the mobility course as an endpoint in clinical trials
	Pediatric (ongoing)	Safety and tolerability in children < 8 yrs age
	**Phase 2/3 (ongoing)**	**Potential pivotal trial in ≥ 8 yrs age**

Sepofarsen pivotal Phase 2/3 trial

Enrollment complete Jan. 2021; topline data expected late Q1/early Q2

Illuminate



Key inclusion criteria:

- LCA10 due to the c.2991+1655A>G mutation in the *CEP290* gene
- Age ≥ 8 years
- BCVA = 0.4 to 3.0 logMAR (20/50-HM)

Study design:

- Multicenter, Randomized, Double-Masked, Sham controlled phase 2/3 study

Primary Endpoint:

- Change from baseline in BCVA (logMAR) at Month 12

Secondary Endpoints:

- Mobility course
- Full field stimulus testing (FST)
- Optical coherence tomography (OCT)

Illuminate – statistical overview

- **Primary Endpoint:** Change from baseline at Month 12 in BCVA (logMAR) in the treated eye compared to sham
- **Primary Analysis:** ANCOVA, baseline BCVA as a covariate (to control baseline BCVA differences across subjects); adjusted for multiplicity
  - Sepofarsen 160/80 µg versus Sham
  - Sepofarsen 80/40 µg versus Sham
  - (Sepofarsen 160/80 µg + sepofarsen 80/40 µg) versus Sham
- **Sample Size:** Originally planned for 30 subjects, *Illuminate* exceeded the enrollment target
  - With a sample size of 36pts, we have >90% power to detect a BCVA change of 0.3 logMAR (Primary Analysis), with an alpha of 0.05.

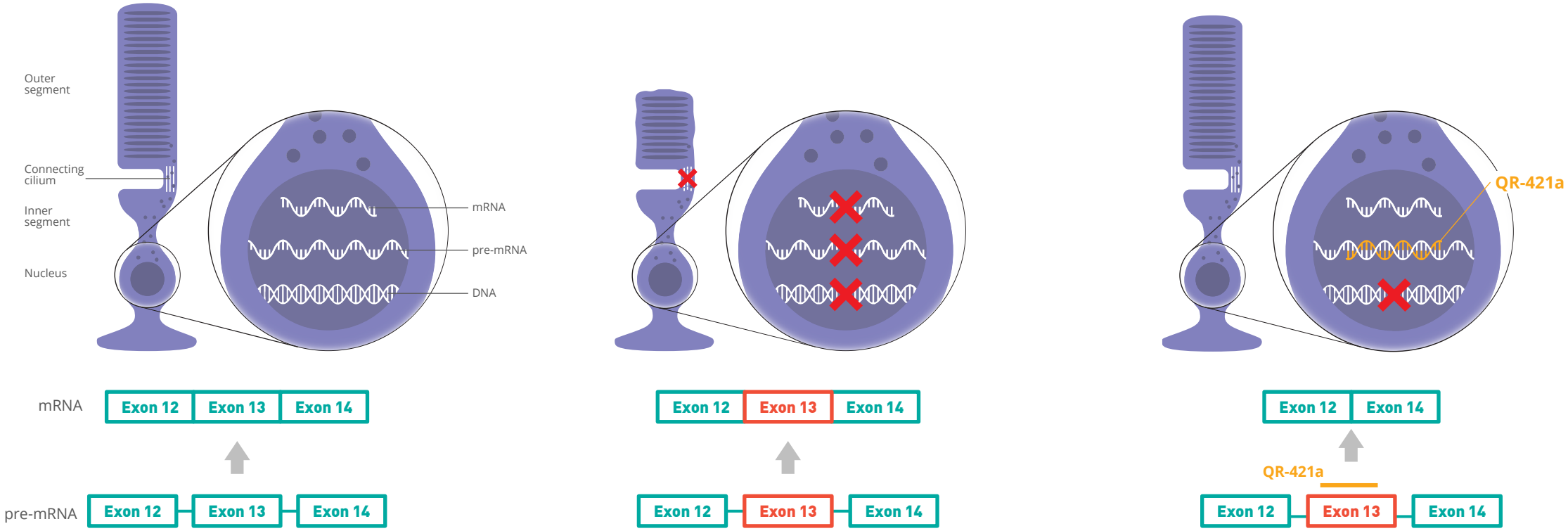
Sepofarsen for *CEP290*-mediated LCA10

- Robust development program
  - ✓ Completed enrollment in pivotal Phase 2/3 *Illuminate* trial (January 2021)
  - ✓ Started pediatric *Brighten* study (Q2 2021)
  - ✓ *InSight* extension study ongoing
- Top-line readout from pivotal Phase 2/3 *Illuminate* trial in late Q1 / early Q2 2022

QR-421a for retinitis pigmentosa and Usher syndrome

QR-421a for RP and Usher syndrome

Skipping of exon 13 in USH2A RNA



In wild-type cells Ush2A protein enables protein transport through the connecting cilium

In cells with the mutation Ush2A protein is not active hampering protein transport through the cilium

Exclusion of mutated exon leads to restoration of functionality of Ush2a

QR-421a for *USH2A*-mediated RP

Designed to treat genetic vision loss in Usher syndrome & retinitis pigmentosa

RNA therapy for Usher & nsRP

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. Approximately 15-25% has exon 13 mutations on both alleles

Partnership

Awarded $7.5M financial support from FFB to conduct trial

Unmet need

Potential first-in-class RNA therapy targeting ***USH2A* exon 13** mutations

- Strong preclinical proof of concept in patient-derived retinal model
- Orphan drug designation & Rare pediatric disease designation
- Fast track designation
- *Stellar* Ph 1/2 trial showed signs of efficacy (BCVA/Static Perimetry/OCT), and manageable safety
- Two pivotal Phase 2/3 trials – *Sirius* and *Celeste* – to start before year end 2021

Clinical trials for QR-421a

	Trial phase	Trial objectives
STELLAR	Phase 1/2 (completed)	Safety & tolerability
HELIA	Phase 1/2 extension (ongoing)	Continued treatment for *Stellar* patients, multiple dose & 2nd eye treatment
SIRIUS	Phase 2/3 in advanced (planned)	Potential pivotal trial for patients with advanced vision loss
CELESTE	Phase 2/3 in early-moderate (planned)	Potential pivotal trial for patients with early to moderate vision loss

Clinical trials for QR-421a

	Trial phase	Trial objectives
STELLAR	**Phase 1/2 (completed)**	**Safety & tolerability**
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CELESTE	Phase 2/3 in early-moderate (planned)	Potential pivotal trial for patients with early to moderate vision loss

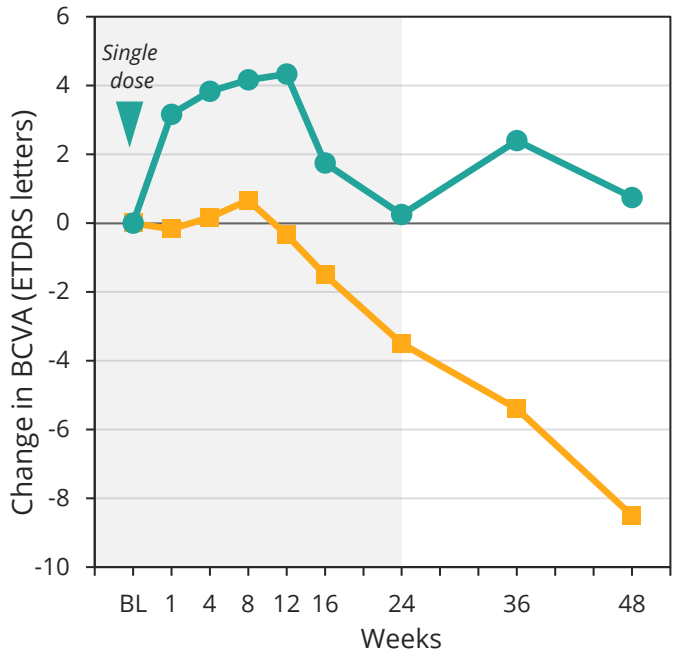
QR-421a *Stellar* Phase 1/2 safety summary

- **QR-421a was well tolerated in >3,700 subject follow up days**
- **No SAEs, no inflammation**
- Cataracts occur in >30% patients in natural history of disease
  - 1 patient had worsening of pre-existing cataracts in both the treated and untreated eye with cataract extractions in both eyes
  - Deemed not treatment related by Investigator
- Cystoid Macular Edema (CME) known to occur as part of natural history of disease in >30% of the patients
  - No new occurring cases of CME during study
  - 1 patient with CME at baseline progressed during study, classified as mild, managed with standard of care

Summary of Phase 1/2 *Stellar* trial results

Redosing interval established at 6 month

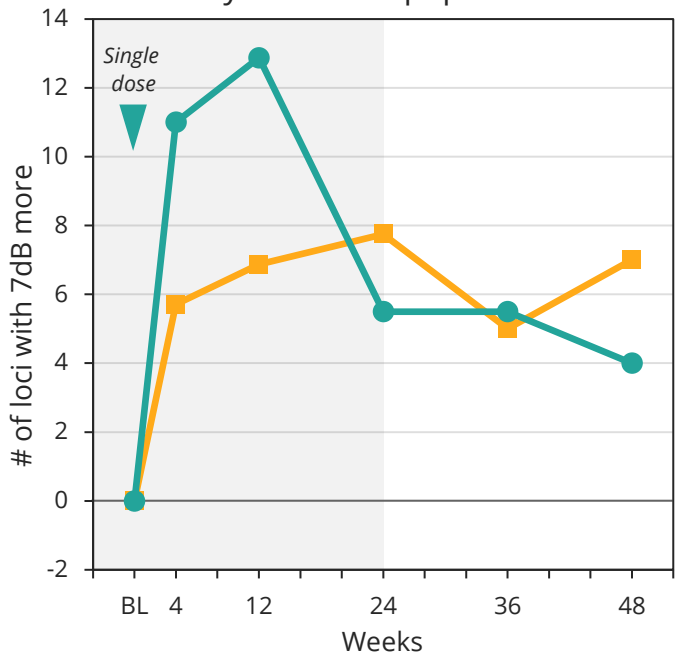
Mean Change from Baseline in BCVA
Advanced Population



Phase 2/3 *Sirius* trial

- Advanced population
- Primary endpoint BCVA

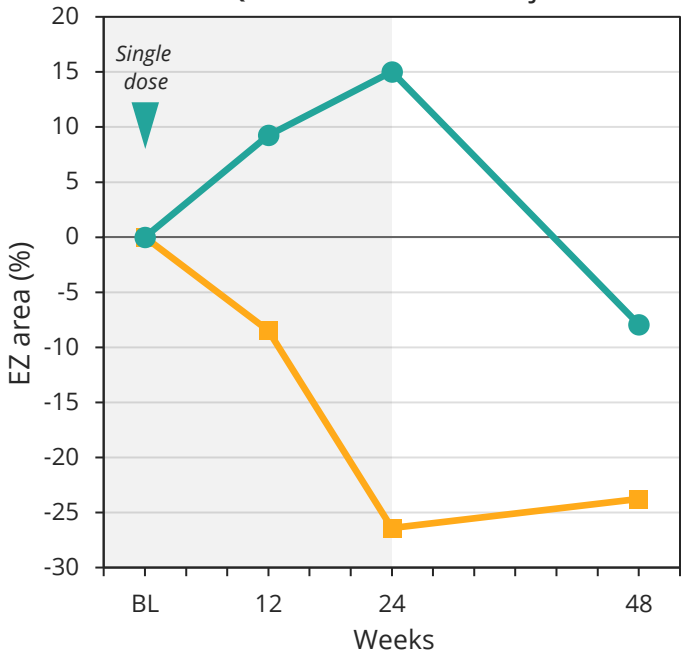
Mean Number of retinal loci with ≥7dB improvement in static perimetry
Early-moderate population



Phase 2/3 *Celeste* trial

- Early to moderate population
- Primary endpoint static perimetry

Ellipsoid zone area:
% mean change from baseline
All QR-421a treated subjects



QR-421a Treated eye

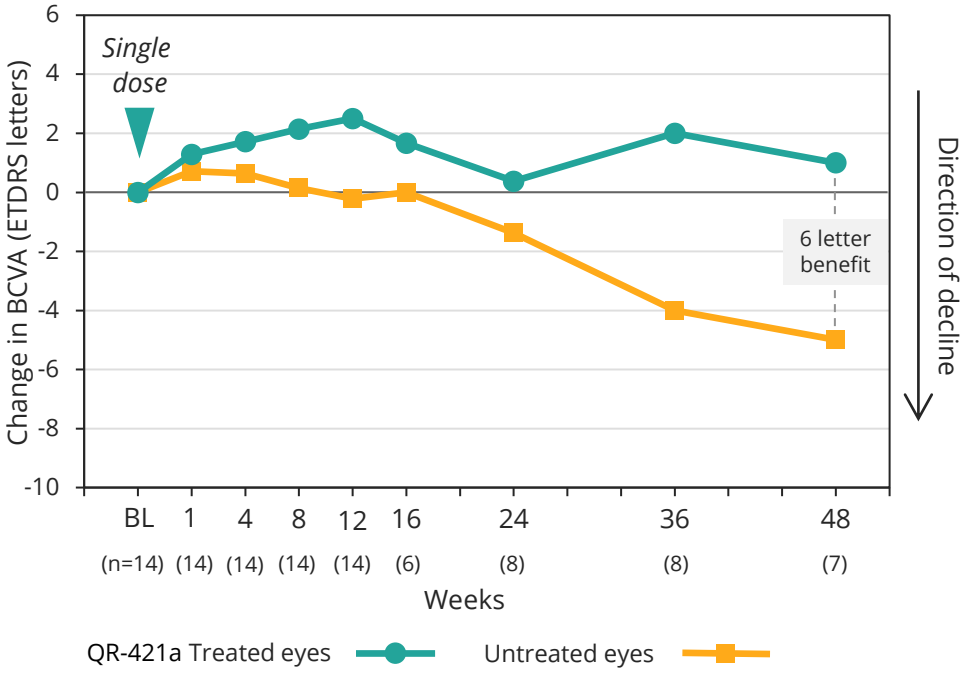
Untreated eye

BCVA stabilization in all treated eyes

Mean change from baseline in BCVA after single injection

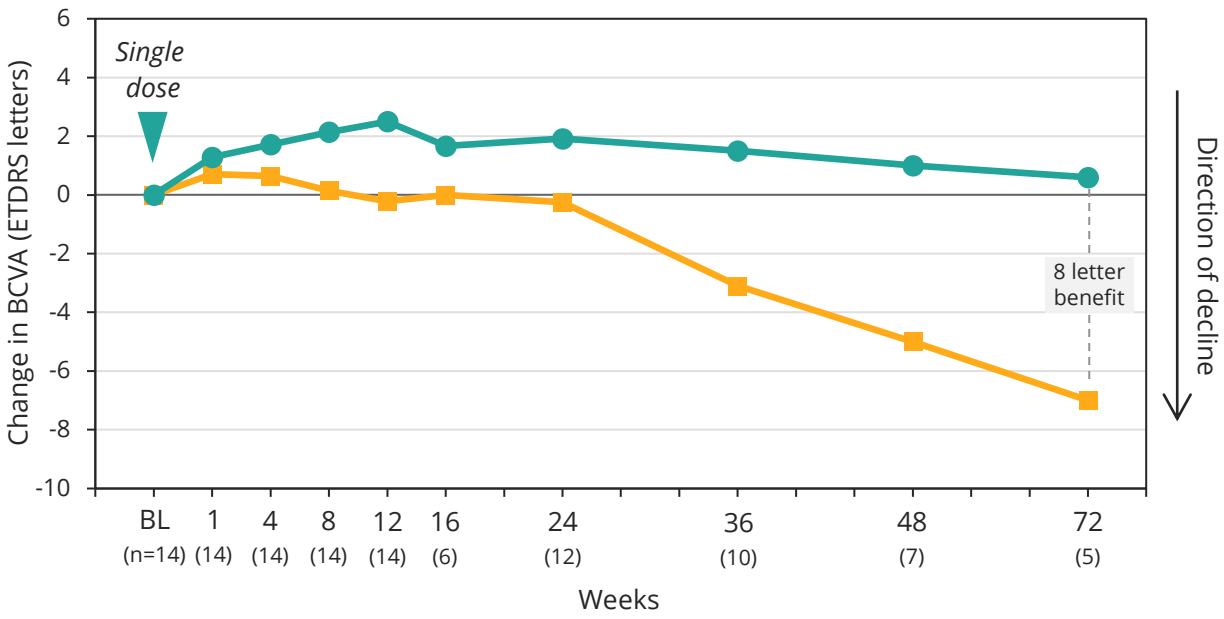
Mean 6 letter benefit at week 48

All QR-421a treated patients (n=14)



Mean 8 letter benefit at week 72

All QR-421a treated patients (n=14)



- Stabilization of vision observed in treated eye vs decline in untreated eye in all patients
- Deterioration of untreated eye in line with natural history

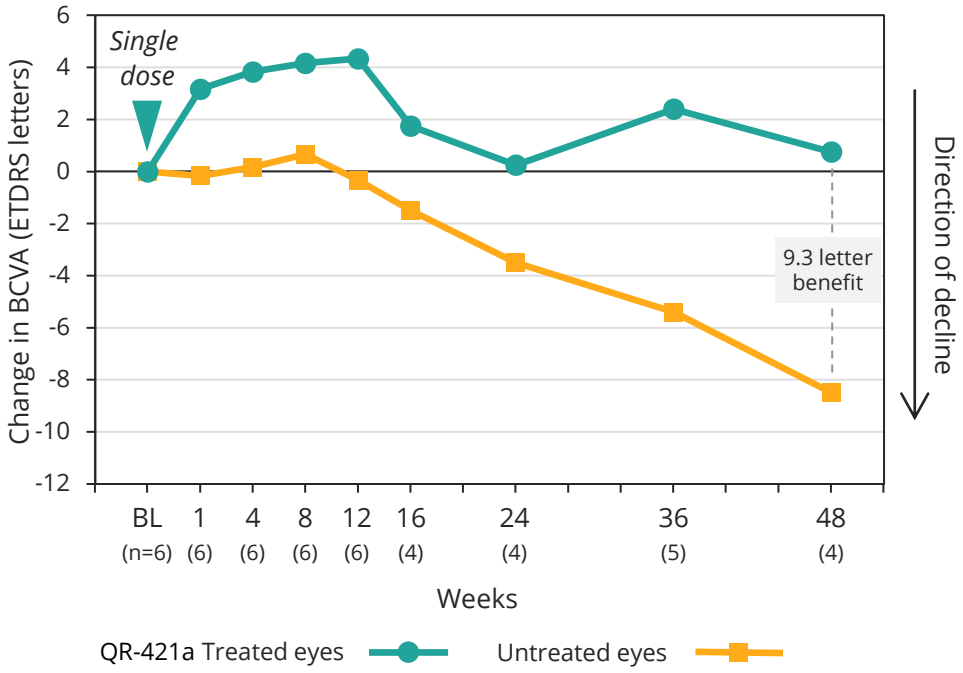
- 6 letter benefit at week 48, after single dose
- 8 letter benefit at week 72
- Sustained effect consistent with long half-life of QR-421a

BCVA stabilization driven by advanced population

Mean change from baseline in BCVA after single injection

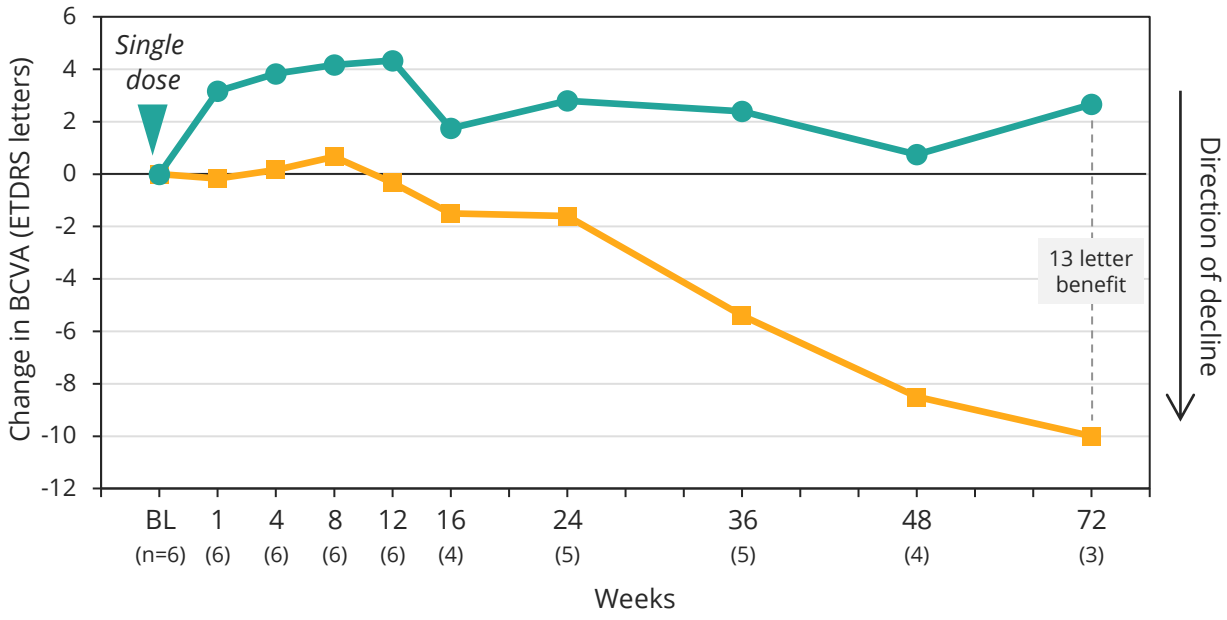
Mean 9.3 letter benefit at week 48

Advanced population (n=6)



Mean 13 letter benefit at week 72

Advanced population (n=6)



- BCVA response is driven by advanced disease population
- Stabilization of vision in treated eye after single dose
- Mean 9.3 letter benefit at week 48
- Mean 13 letter benefit at week 72
- Sustained effect is consistent with long half-life of QR-421a
- Week 72 is Primary Endpoint timepoint in *Sirius* (Ph 2/3) Study

Clinical trials for QR-421a

	Trial phase	Trial objectives
STELLAR	Phase 1/2 (completed)	Safety & tolerability
HELIA	**Phase 1/2 extension (ongoing)**	**Continued treatment for *Stellar* patients, multiple dose & 2nd eye treatment**
SIRIUS	Phase 2/3 in advanced (planned)	Potential pivotal trial for patients with advanced vision loss
CELESTE	Phase 2/3 in early-moderate (planned)	Potential pivotal trial for patients with early to moderate vision loss

Helia extension trial

Open label, extension trial for Phase 1/2 participants

Objectives

- Generate further safety and efficacy data for *Stellar* patients
- Repeat dose & 2nd eye treatment (180 µg loading dose followed by 60 µg every 6 months) for both eyes

Status

- Started to roll over *Stellar* participants into *Helia* study

Next steps

- Update from *Helia* extension trial by year end 2022

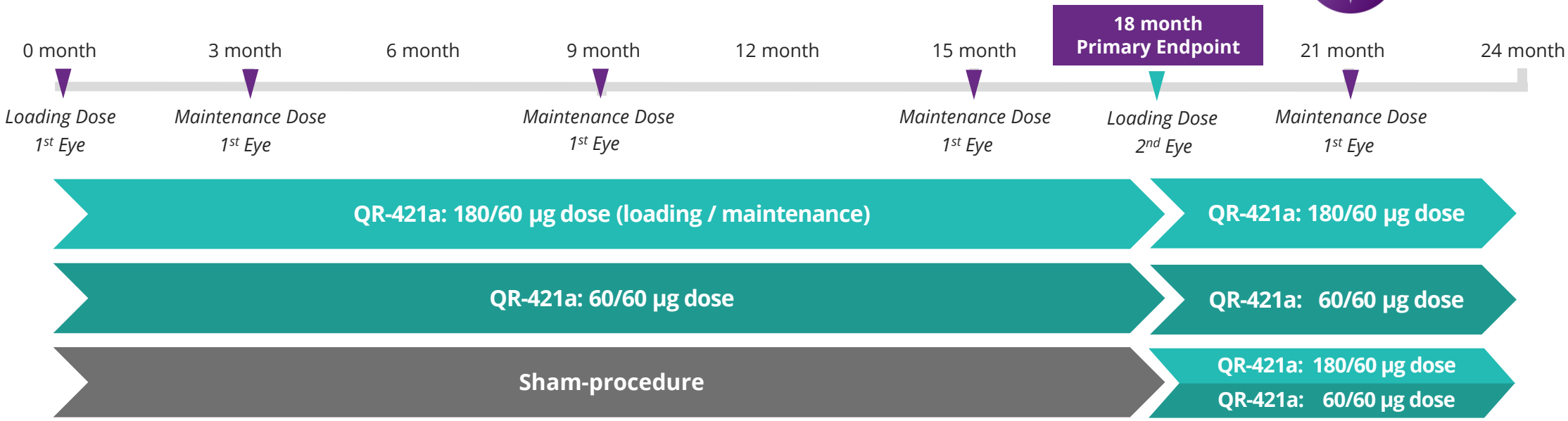
Clinical trials for QR-421a

	Trial phase	Trial objectives
STELLAR	Phase 1/2 (completed)	Safety & tolerability
HELIA	Phase 1/2 extension (ongoing)	Continued treatment for *Stellar* patients, multiple dose & 2nd eye treatment
SIRIUS	**Phase 2/3 in advanced (planned)**	**Potential pivotal trial for patients with advanced vision loss**
CELESTE	**Phase 2/3 in early-moderate (planned)**	**Potential pivotal trial for patients with early to moderate vision loss**

QR-421 Phase 2/3 trial for *Advanced Patients*

Final design as agreed with Regulators

SIRIUS

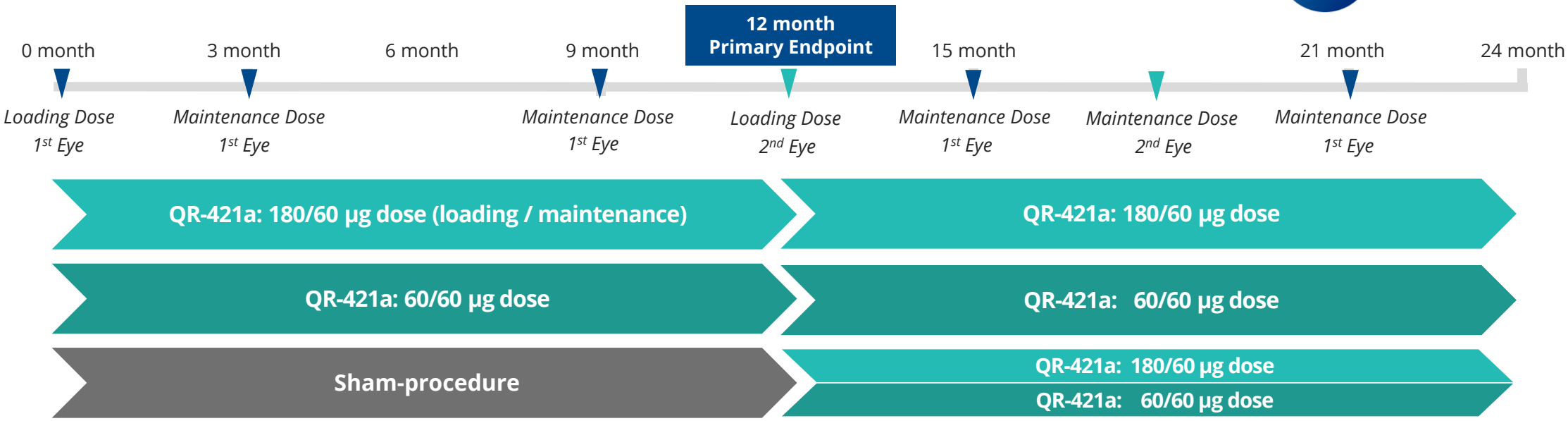


- Double-masked, randomized, sham controlled, 24-month, multiple dose study
- Population:
  - Approx. 80 patients (age ≥ 12 years)
  - Homozygous and heterozygous, Usher and RP
  - Baseline BCVA 30 - 68 ETDRS letters in study eye (< 20/40)
- Primary endpoint: Change from baseline in BCVA at month 18, versus sham
- Key secondary endpoint: Proportion of patients who maintain vision (BCVA loss < 15 ETDRS letters)
- Other endpoints: BCVA, Ellipsoid Zone (SD-OCT), FST, Perimetry, Mobility, Patient Reported Outcomes
- **Anticipated start of trial: Year end 2021**

QR-421 Phase 2/3 trial for *Early-Moderate Patients*

Final design as agreed with Regulators

CELESTE



- Double-masked, randomized, sham controlled, 24-month, multiple dose study
- Population:
  - Approx. 120 patients (age ≥ 12 years)
  - Homozygous and heterozygous, Usher and RP
  - Baseline BCVA ≥ 69 ETDRS letters in study eye (≥ 20/40)
- Primary endpoint: Change from baseline in mean sensitivity using static perimetry at month 12, versus sham
- Key secondary endpoint: Ellipsoid Zone area as measured by SD-Ocular Coherence Tomography (OCT)
- Other endpoints: BCVA, FST, Perimetry, Mobility, Patient Reported Outcomes
- **Anticipated start of trial: Year end 2021**

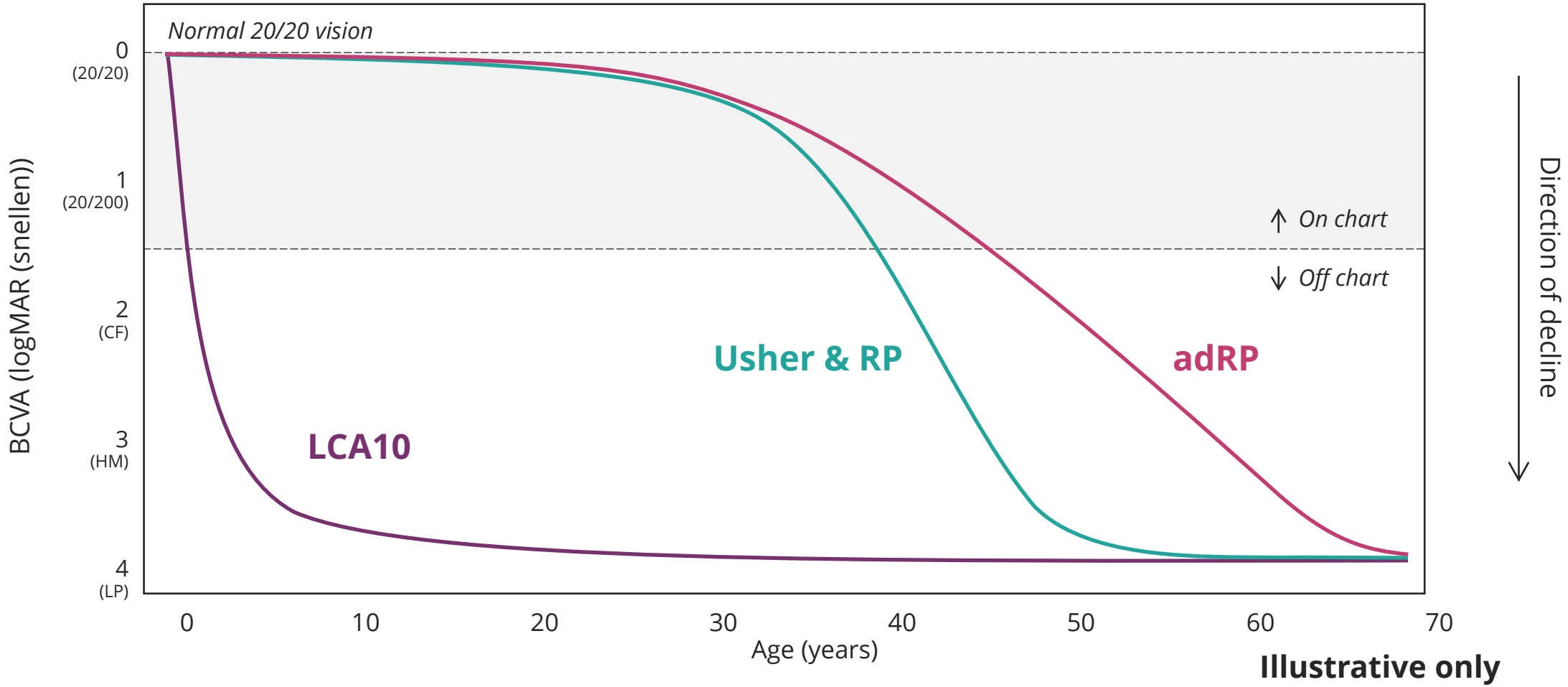
QR-421a for Usher syndrome and RP

- Phase 1/2 *Stellar* study completed - participants rolled over into *Helia* extension study
- On track to start pivotal Phase 2/3 *Sirius* and *Celeste* trials by year end
- Update from *Helia* extension trial by year end 2022

QR-1123 for autosomal dominant retinitis pigmentosa

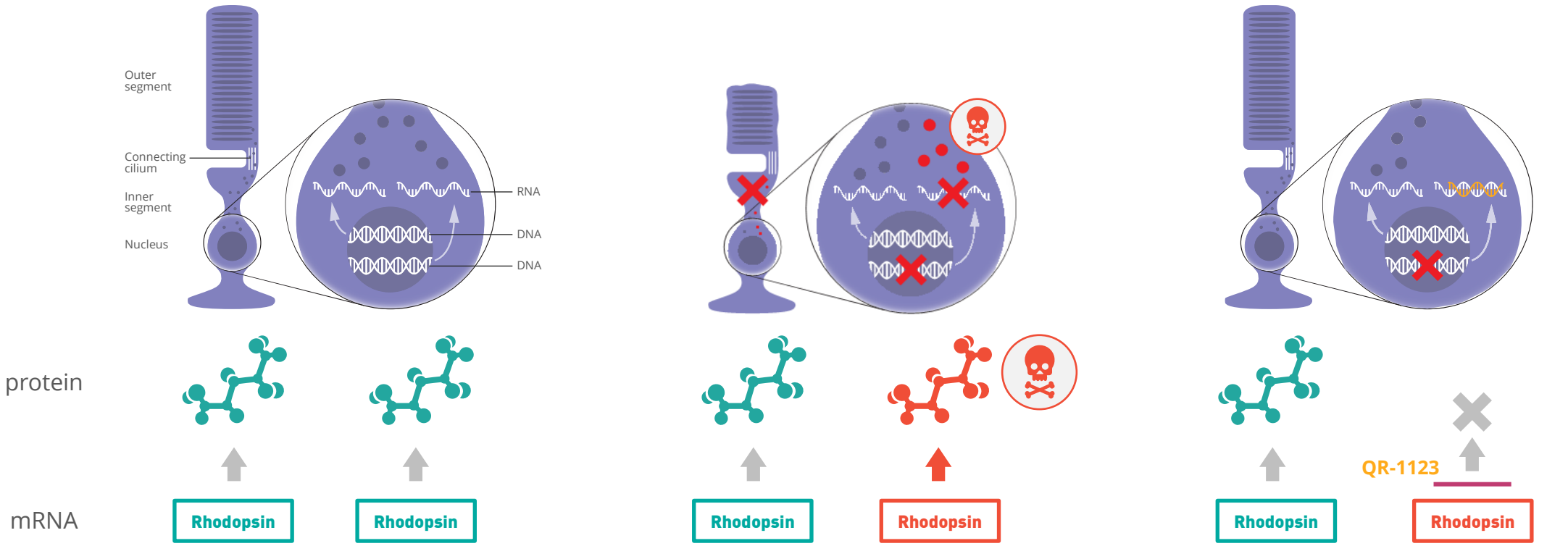
Visual acuity loss in selected IRDs

Individuals with adRP will eventually go completely blind, though disease progression is slower than Usher/RP and LCA10



QR-1123 mechanism of action

Blocks expression of toxic P23H mutant RHO protein



Healthy people inherit two wild type copies of the rhodopsin gene

P23H mutant rhodopsin is misfolded and toxic, causing progressive loss of rods

QR-1123 suppresses P23H mRNA with an allele specific mechanism

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

RNA therapy: QR-1123

Goal: Restore vision/prevent vision loss in patients with P23H adRP

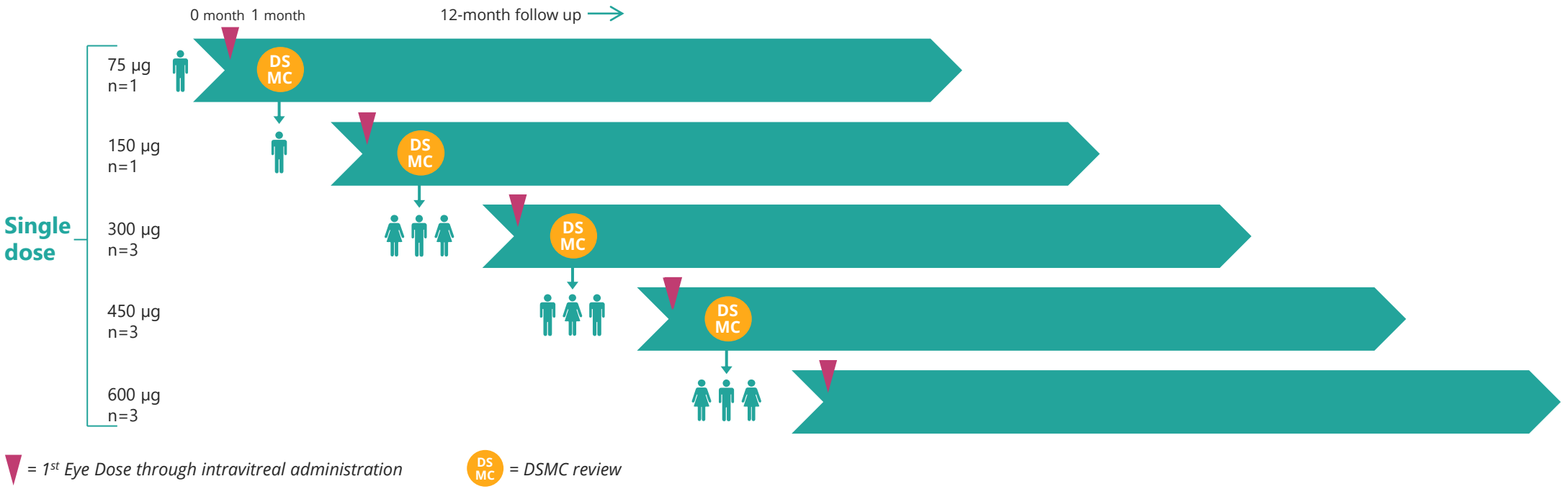
Locally administered in the eye. Routine intravitreal procedure

Optimizing dosing frequency

- ✓ Established modality in eye
- ✓ Strong preclinical proof of concept in vivo
- ✓ In-licensed from Ionis Pharmaceuticals
- ✓ 2-year Natural History Study
- ✓ Orphan drug designation
- ✓ Ph 1/2 study showed target engagement and manageable safety after single injection
- • Repeated dose Phase 2 study to start in 2022

QR-1123 Phase 1/2 trial in adRP patients

Single ascending dose



***Aurora* Phase 1/2 trial**

- Goals include safety, tolerability and efficacy signal
- Initial data from dosing cohorts (n=11)

Key endpoints include:

- Visual acuity
- Visual field
- Microperimetry
- EZ area (OCT)

Aurora

QR-1123 Phase 1/2 safety summary

Single dose Aurora study

Objective of study was met

- Manageable safety profile observed
- QR-1123 is well tolerated
- No SAEs observed
- No cases of retinal thinning
- Cataracts
  - 9 of 11 patients had cataracts in both eyes at baseline
  - 3 cases of cataract worsening were observed
- Cystoid macular edema (CME)
  - 7 of 11 patients had CME (or retinal cysts) at baseline in one or both eyes
  - CME was more frequent in 450 - 600 µg doses (4 of 6 treated eyes) than 75 - 300 µg doses (2 of 5 treated eyes)

Based on the safety profile the 75 - 300 µg doses are selected for further studies

QR-1123 Phase 1/2 efficacy summary

Single dose Aurora study

- **Target engagement was established** across majority of patients, across different endpoints
- Half life of QR-1123 (gapmer) is 5 weeks
- Maximum benefit in BCVA observed after 5 weeks of treatment and declined thereafter, consistent with the half life of the drug
  - **BCVA at 5 weeks**
    - Across all subjects, the treated eye showed a mean BCVA benefit of +1.4 letters
    - In doses 75 - 300 µg, the mean BCVA benefit was +5 letters, maximum benefit observed was +7 letters
  - **Static perimetry at 5 weeks**
    - Across all subjects, mean total retinal sensitivity improvement (treated eye minus untreated eye) of +50 dB
    - Across all subjects, mean number of retinal loci with ≥ 7 dB improvement from baseline was greater in treated eyes compared to untreated eyes

QR-1123 next steps

Repeated dose Phase 2 study to start in 2022

Key take-aways

- QR-1123 is well tolerated
- Consistent target engagement/efficacy signal with doses 75 µg through 300 µg

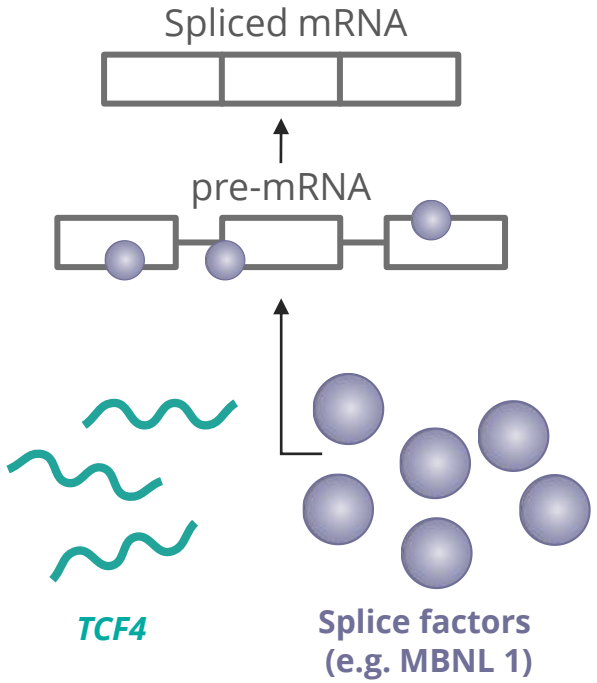
Next steps

- Based on the findings from *Aurora*, a repeated dosing Phase 2 study is planned with doses up to 300 µg
- Endpoints will include BCVA and static perimetry
- Study to start in 2022

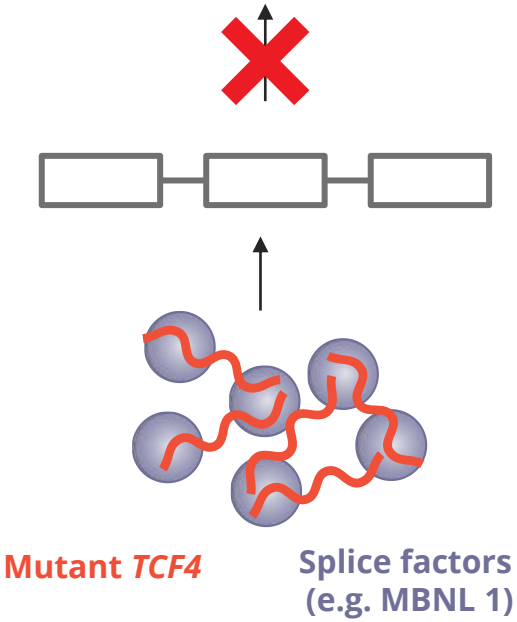
QR-504a for Fuchs endothelial corneal dystrophy

QR-504a mode of action

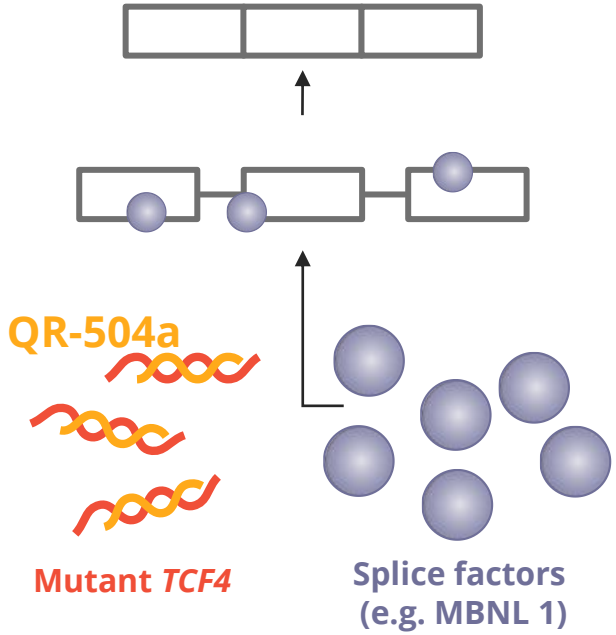
Targets TCF4 repeat expansions to normalize splicing processes



In healthy cells, normal splicing process of pre-mRNAs to mRNAs



TNR expansions in *TCF4* RNA form aggregates (foci) and sequester splice factors, disrupting splicing



QR-504a targets the *TCF4* RNA (foci) and releases splice factors to re-establish splicing of mRNAs

QR-504a for FECD3

Fuchs Endothelial Corneal Dystrophy Type 3

- Corneal disease leading to blindness in mid-adulthood
- Only treatment is corneal transplant
- Genetic disease caused by Trinucleotide Repeat (TNR) expansion (>50 repeats) in ***TCF4***

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

RNA therapy: QR-504a

- QR-504a is designed to be complimentary to mutant *TCF4*, leading to disease stabilization

Strong PoC

- TNR expansion in ***TCF4*** cause global aberrant splicing, eventually leading to endothelial cell death
- In patient explant models, QR-504a normalizes aberrant splicing

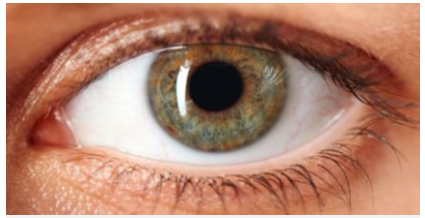
- ✓ RNA is established modality in eye
- ✓ Rapid delivery to corneal cells
- ✓ Strong preclinical proof of concept in human primary cell models

- Trial open
- First data 2022

Corneal endothelial cell loss causes FECD

Underlying molecular mechanism is based on accumulation of abnormally-spliced RNA

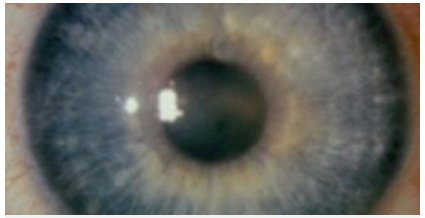
Progressive loss of corneal architecture causes “Glare” and “Photophobia” symptoms



Guttae only – debris of dead cells

Subclinical diagnosis

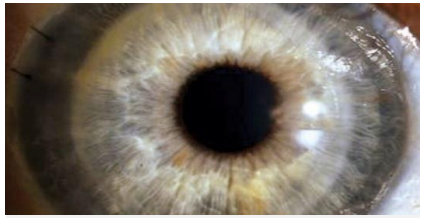
> Diagnosis



Subclinical edema -light scatter

Fluid accumulation

> Trigger to treat



Clinical edema - reduced visual acuity

Advanced loss of normal endothelium

> Transplant surgery

Stromal deterioration

Irreversible corneal opacification

Palliative Care

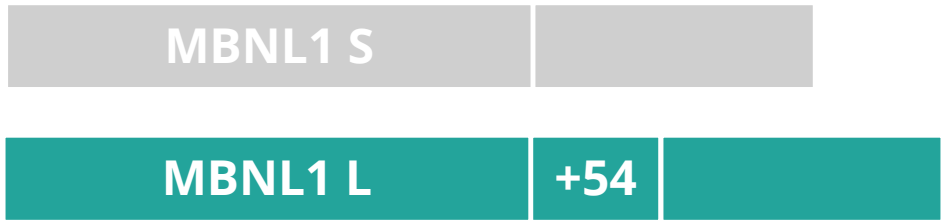
Surgery (DMEK, DSEK)

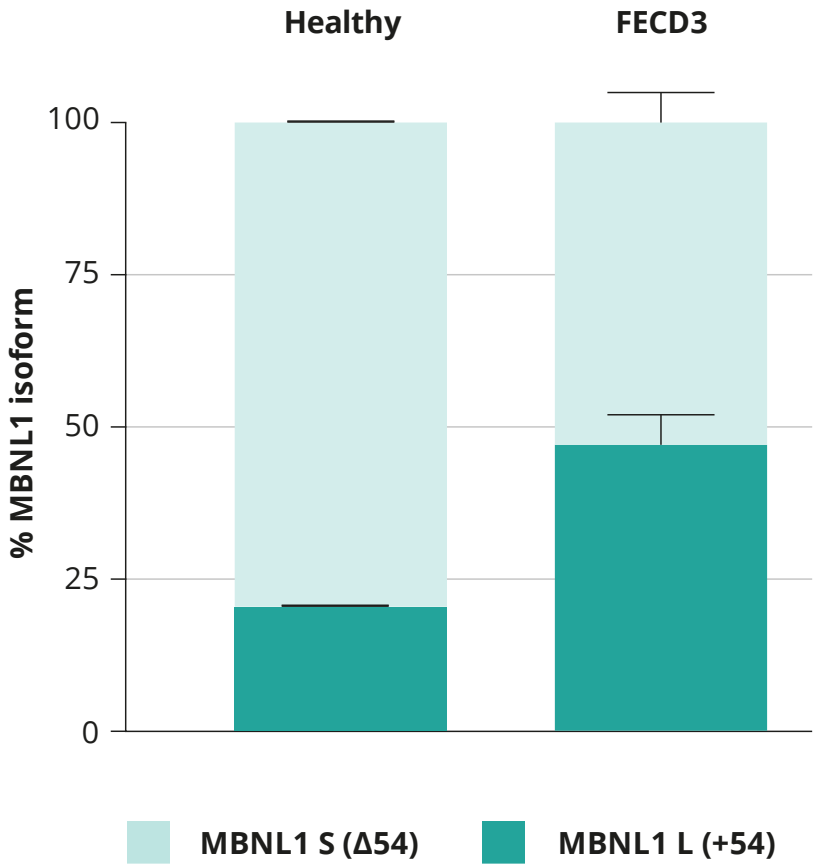
+

MBNL1 example for aberrant splicing in FECD3

Characterization of primary cell models from healthy donors and patients

- Muscleblind Like Splicing Regulator 1 (MBNL1) has 2 isoforms, termed Long (L) and Short (S)
- In patients with FECD3 the ratio of between Long & Short Isoforms is altered
- **Quantifying splice ratio of MBNL1 transcripts serves as Biomarker for FECD3**

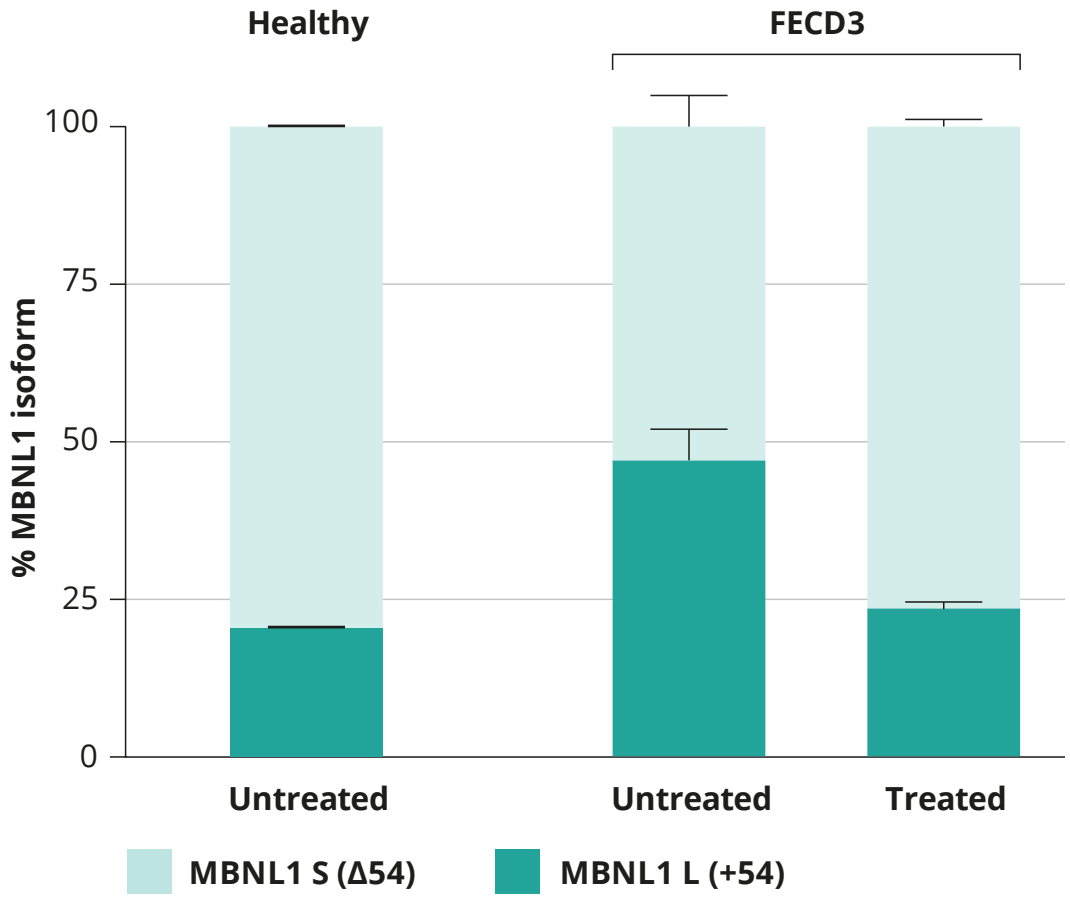




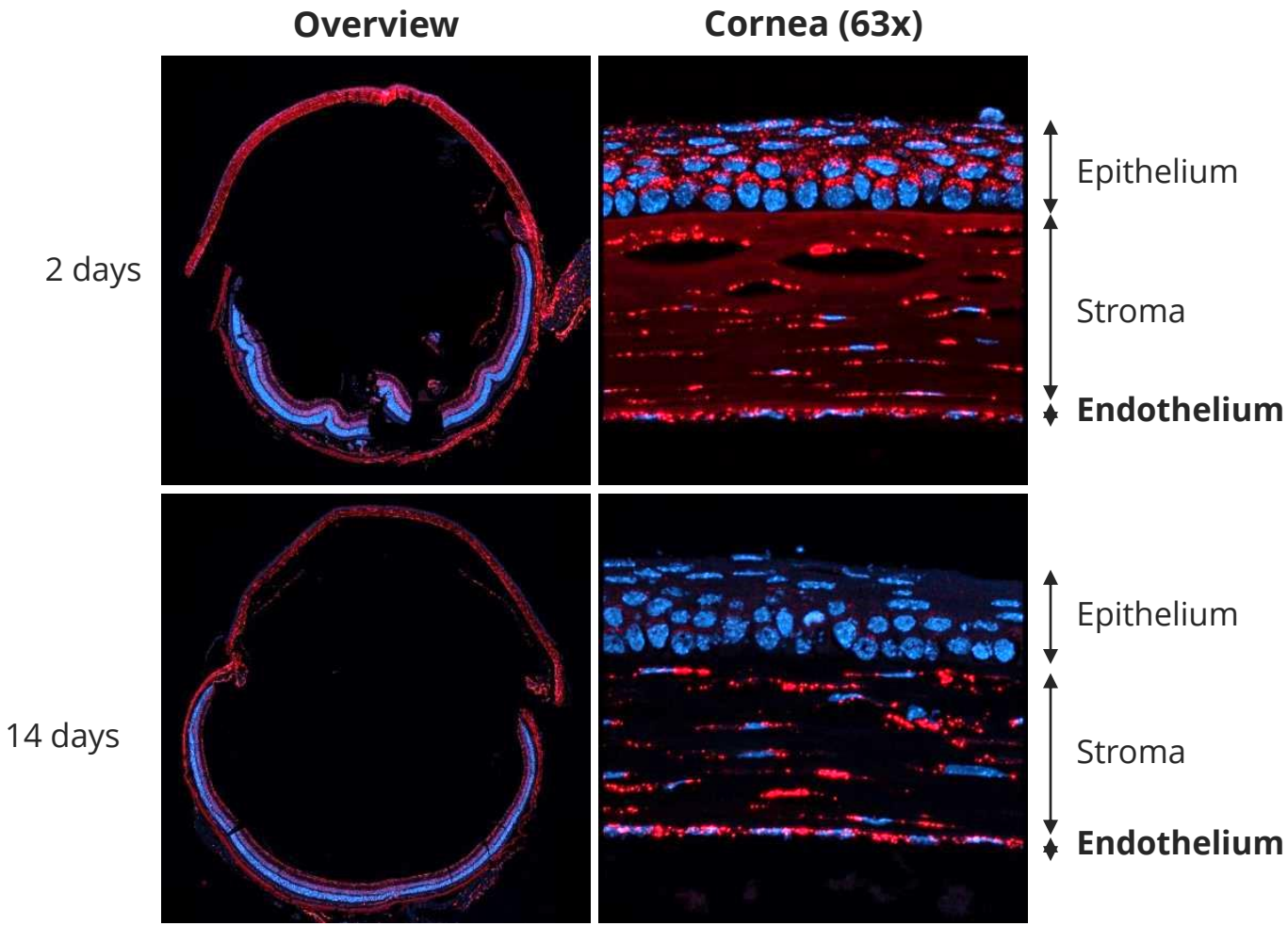
QR-504a treatment to normalize splicing

Isoform ratio of MBNL1 biomarker restored in ex vivo FECD3 primary cells

- QR-504a is complementary to TNR expansions in *TCF4*
- Binding of QR-504a to TNRs results in release of the splicing factors (e.g. MBNL1)
- Reduction in aberrant splicing should prevent RNA mediated toxicity & cell death in FECD3



IVT administered QR-504a shows robust delivery to the corneal endothelium



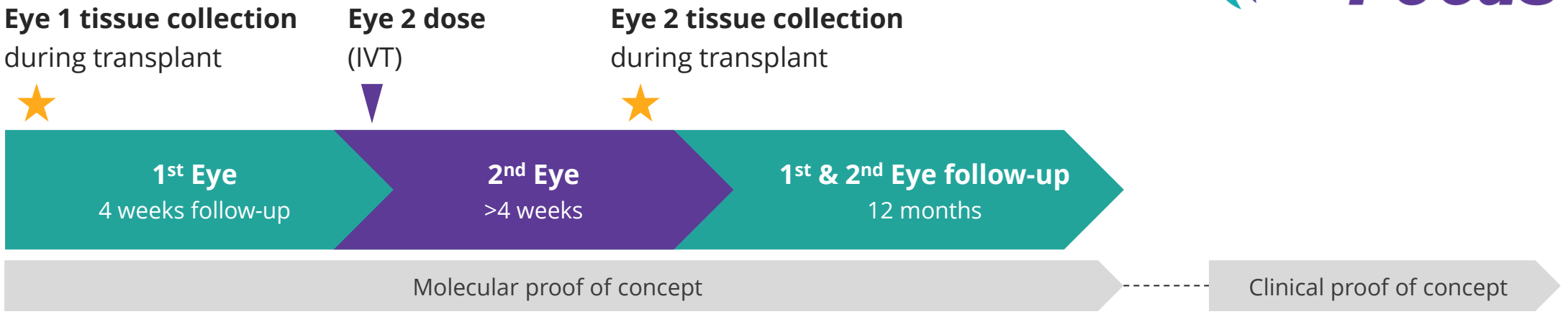
- C57BL/6 mice, m/f (12-14 w)
- Single IVT injection QR-504a (50 µg)
- Detection by Cy5-labeled FISH probe, after 2 days and 14 days post injection, resp.

Blue Nuclear stain (DAPI)
Red Cy5-probe detecting QR-504a

ProQR, unpublished

QR-504a Phase 1b trial in FECD

Molecular proof of concept (PoC) to lead to clinical PoC



***Fuchs Focus* Phase 1b trial**

- Open-label, single-dose, dose escalation, exploratory study
- Goals include safety, tolerability and molecular proof of concept
- Approximately 6 adults
- Trial open, initial data expected 2022

Molecular proof of concept

Biomarker assessment (MBNL 1 short/long form ratio) in corneal tissue removed at surgery for molecular proof of concept

Potential clinical proof of concept

Measure: corneal thickness, visual acuity, fluid build up, QoL

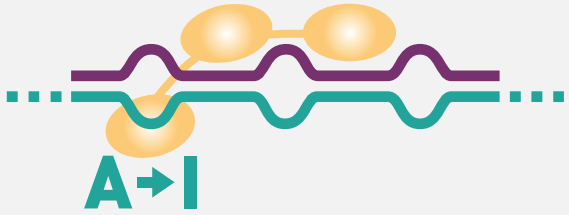
Gerard Platenburg

Chief Innovation Officer

- **Co-founded ProQR** and has served as our Chief Innovation Officer since 2014
- **Extensive background in RNA modulation**, orphan drug discovery & development
- **25 years of senior managerial experience** in growing biotech companies
- **Previously served as Chief Executive Officer** at Isa Pharmaceuticals
- **Co-founded Prosensa** and held various positions including Chief Executive Officer and Chief Development Officer

RNA toolbox – editing platform technologies

Axiomer® and Trident® invented by ProQR



Axiomer® A-to-I editing

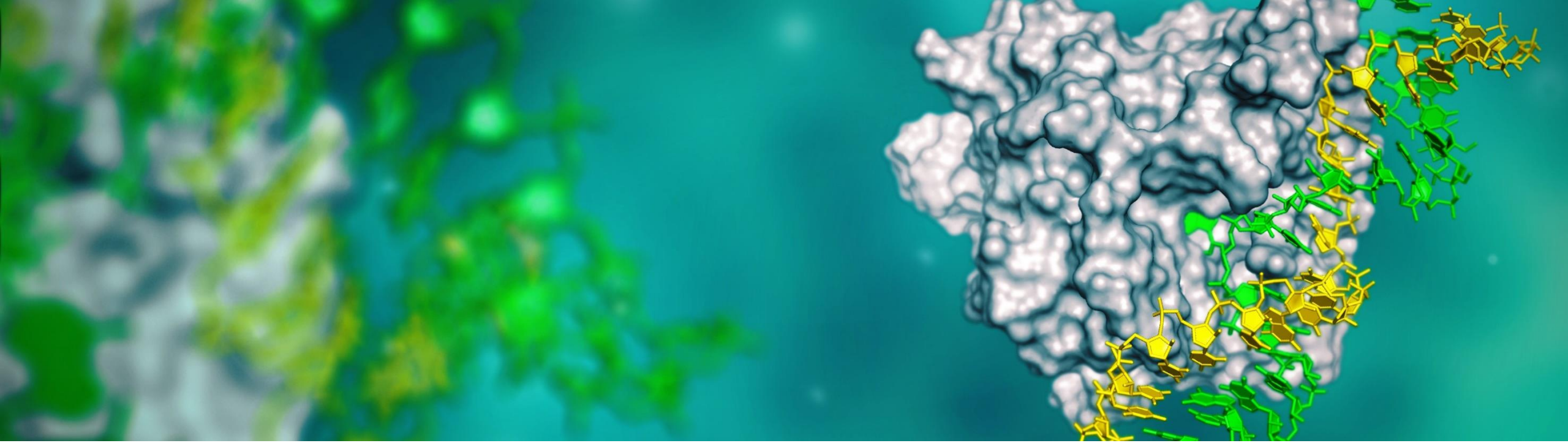
- Exploiting endogenous ADAR
- Recruited by synthetic Editing Oligonucleotide (EON)
- I is translated as a G, allowing to target G-to-A mutations
- Specific, potent, and stable by design
- >20,000 G-to-A mutations described in literature

Trident® U-to-Ψ editing

- Exploiting endogenous pseudouridylation machinery
- Recruited by single stranded pseudouridylation EON (psEON)
- Specifically target PTC mutations (~11% of all known disease-causing mutations)
- Broad applicability in RNA and protein engineering

Strong IP protection

- Foundational patents owned or exclusively licensed by ProQR
- Unrivaled know how on EON/psEON design and high-throughput assays
- Key collaborations with academic experts

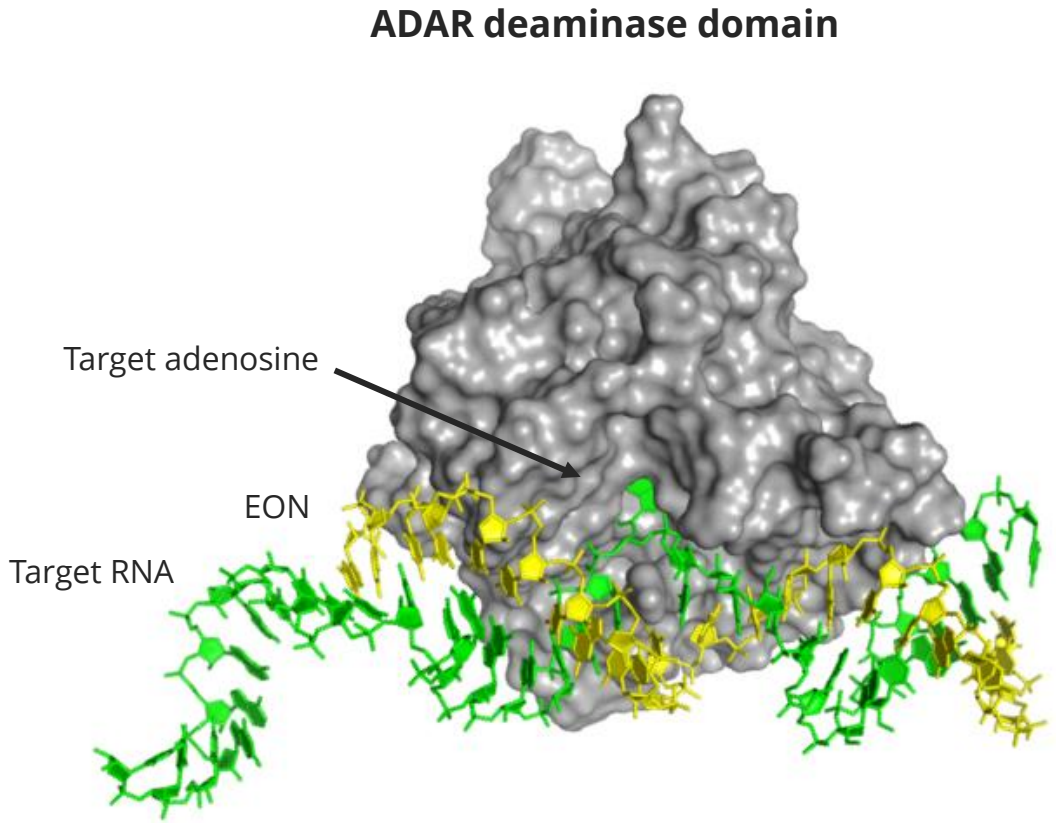


Axiomer®

A-to-I RNA Editing platform

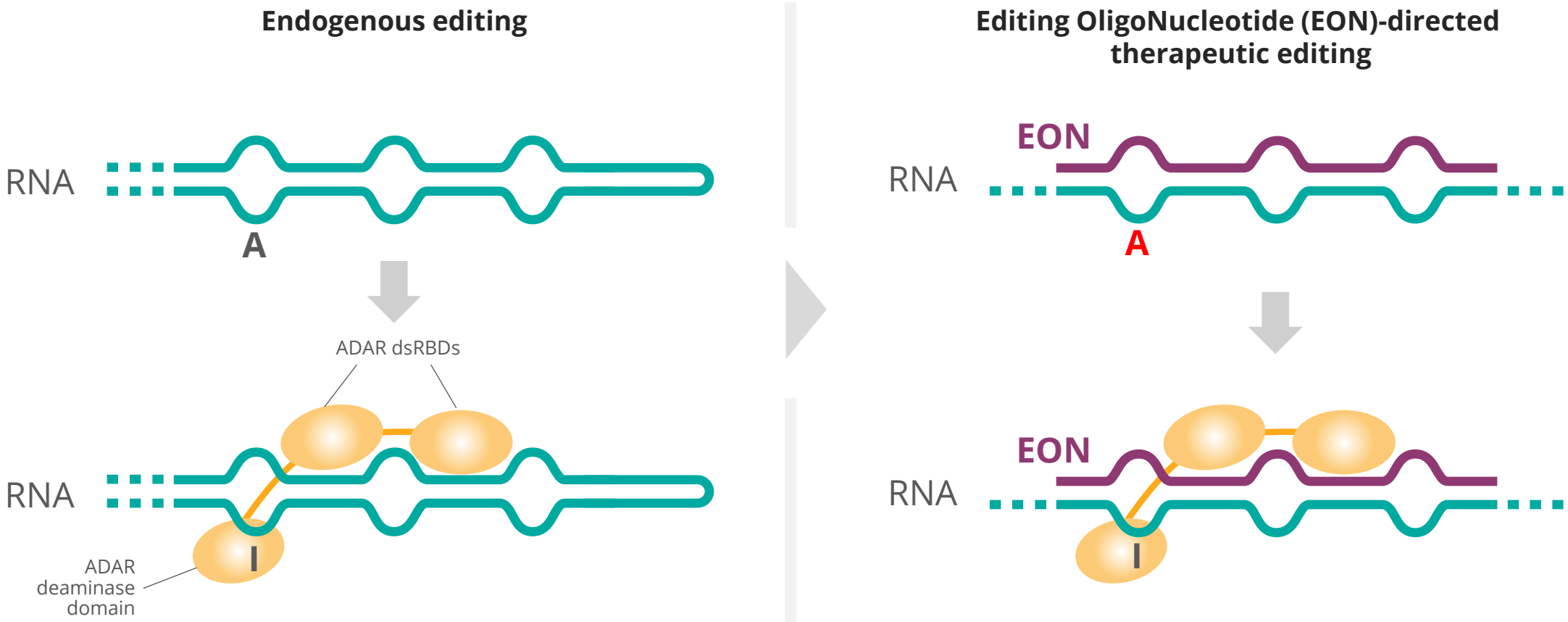
ADAR is the body's own system to edit RNA

- ADAR = **A**denosine **D**eaminase **A**cting on **R**NA
- ADAR is an RNA editing system that is present in all human cells
- In the human body, ADAR is responsible for editing RNA to, for example,
  - Create different isoforms of proteins
  - Change functionality of small RNA molecules
  - Regulate splicing



EONs designed to recruit endogenous ADAR

ADAR deaminates target A in EON-target RNA complex



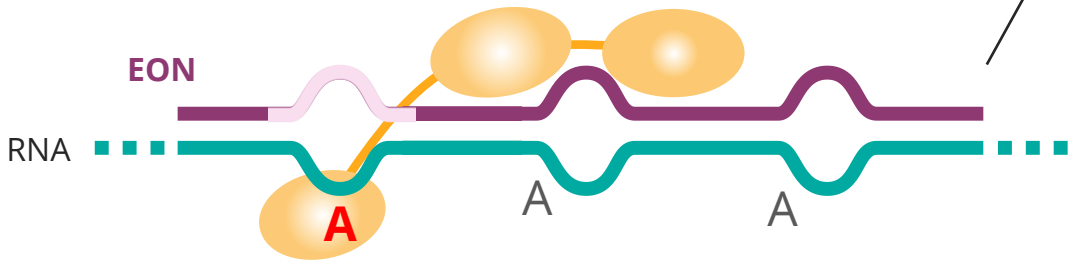
EONs designed for targeted RNA editing

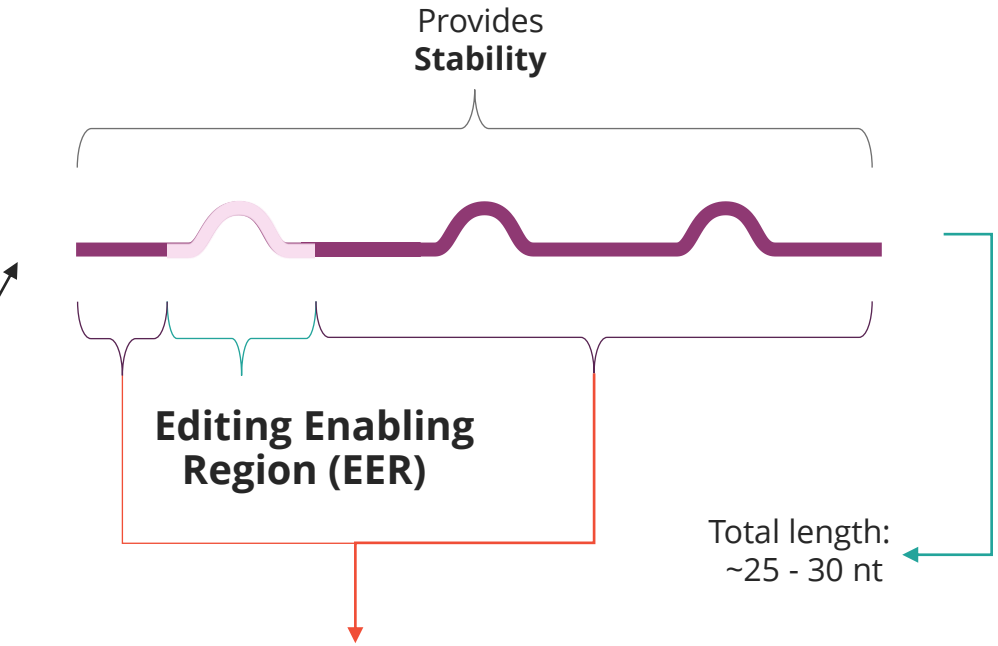
Functionality defined by sequence and chemistry

Sequence defines target RNA binding

EON chemical modifications define:

- Editing efficacy
- Editing specificity
- Stability (nuclease resistance)
- Cell and tissue uptake

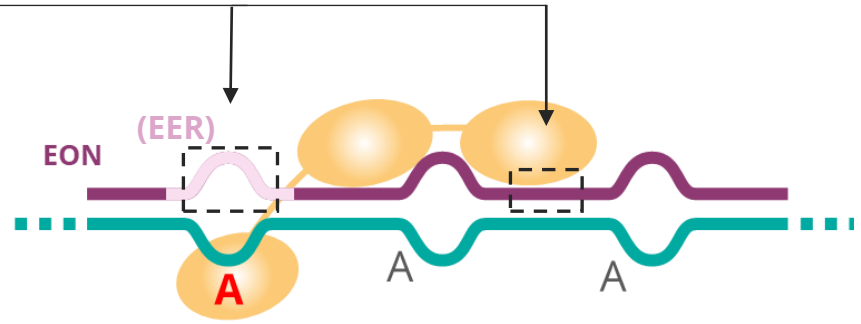




Optimizing EONs for therapeutic use

Separate screening for potency, stability and bioavailability

Challenge: Replace defined **regions** in EONs with new chemical modifications, without compromising ADAR binding and activity.



EON design

Selection of new modifications based on structural analysis and modelling: Fit with ADAR binding

High-throughput screening

Efficacy optimization: Biochemical editing assay

Stability optimization: Biochemical stability assays

Validation phase

Cell-based assays

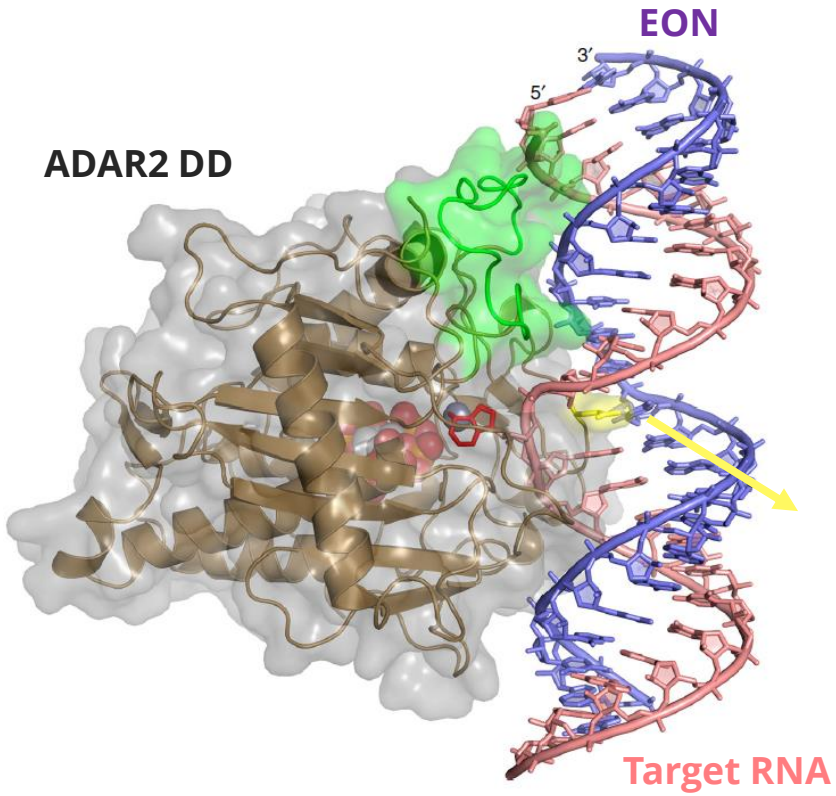
Further development

Single nucleotide modification

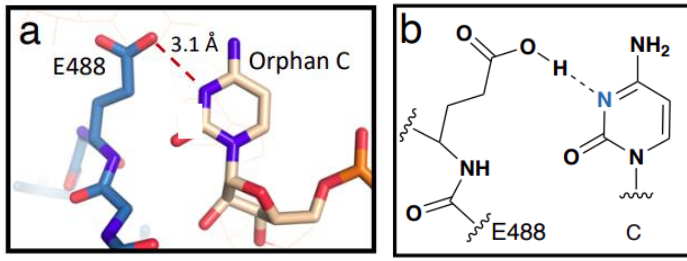
Within EER increases EON efficacy

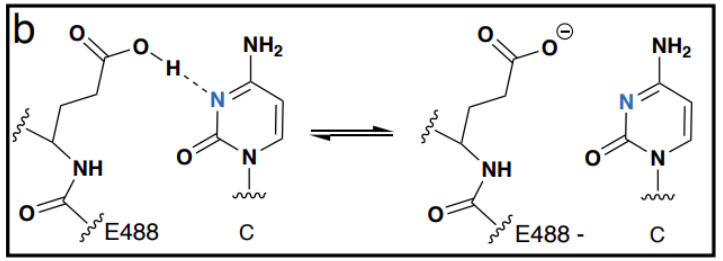
Modification improving EON efficacy identified

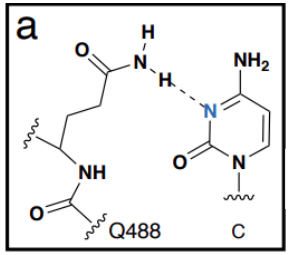
Mimicking E488Q mutation in ADAR2 causing hyperactivity



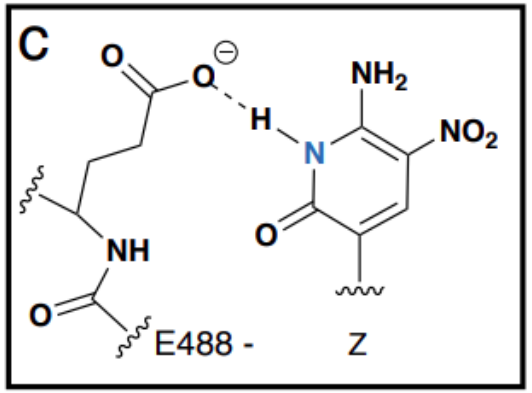
Protonation dependent hydrogen bond – pH dependency







Protonation independent hydrogen bond



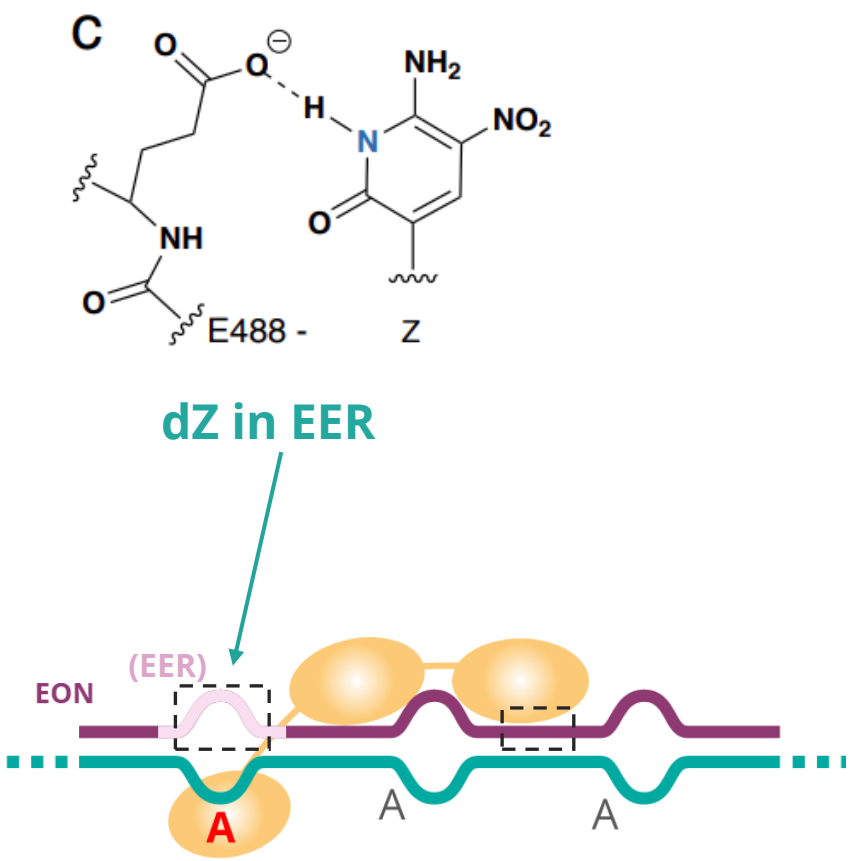
dZ base (dZ)

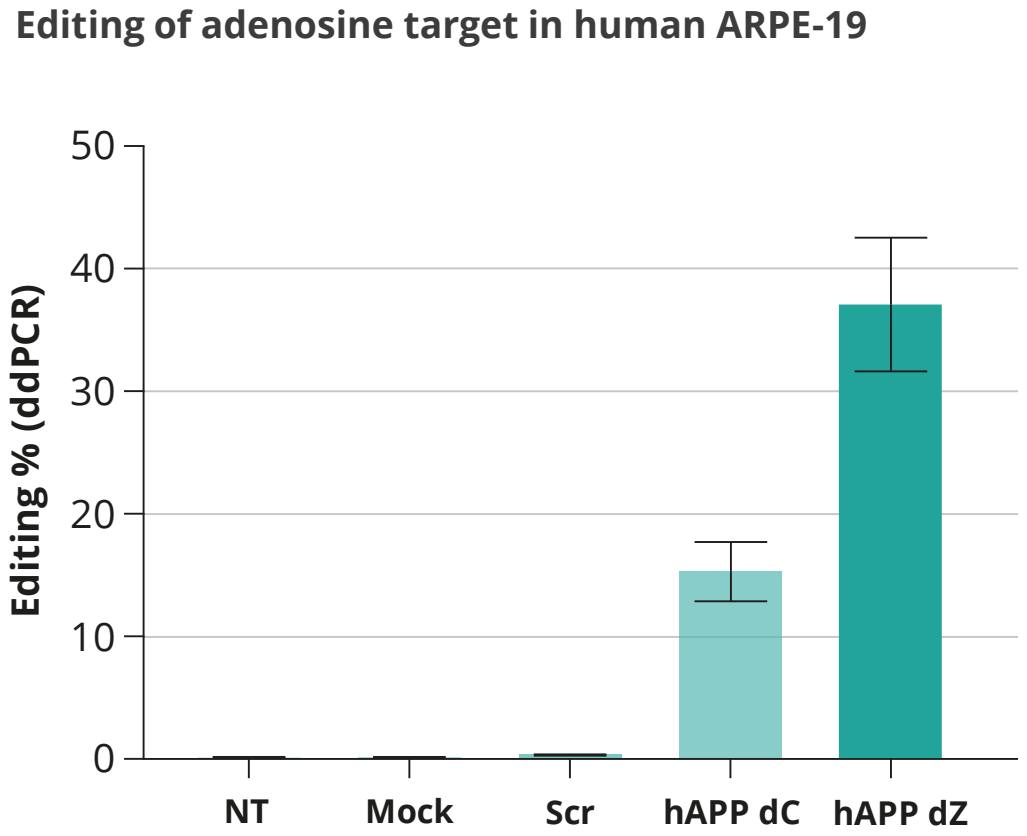
Metthews 2016, Nature Structural & Molecular Biology

Doherty et al., 2021, JACS, ProQR – UC Davis collaboration

dZ base (dZ) modification of the EER

dZ improves editing in human retinal pigment epithelial cells



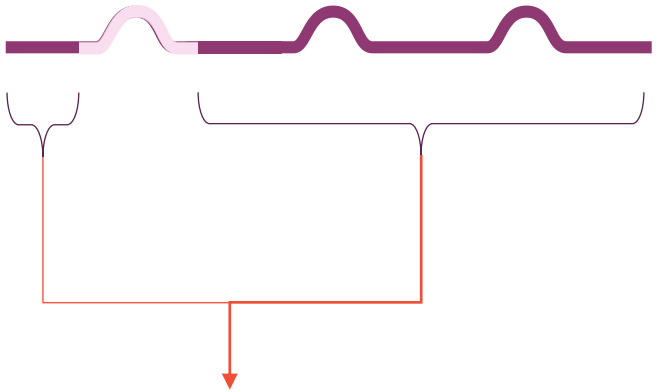


New chemical optimization

For EON ABR region

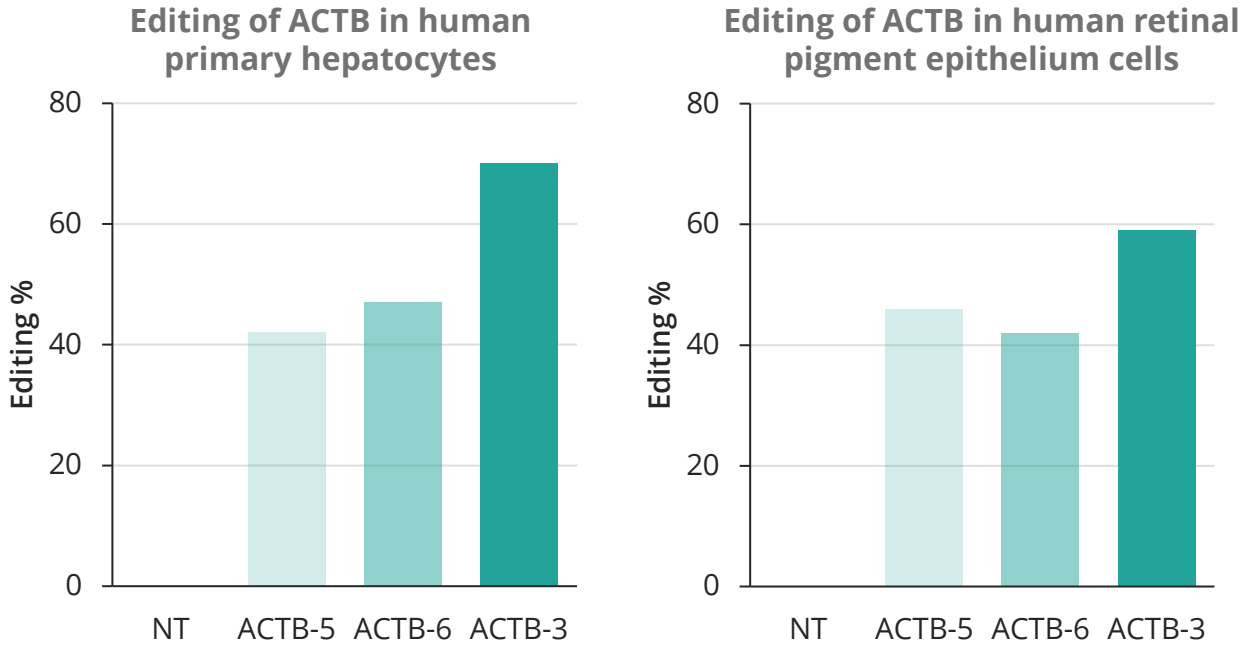
New chemical modification of the ABR

ABR modification greatly enhances editing



Backbone modifications enable ADAR binding, and **improve** stability

ADAR-binding region (ABR)



- Chemical optimization greatly increases EON editing in positions within ABR region
- SAR screen of 2nd backbone modification for best position within ABR region ongoing

Development of Axiomer®

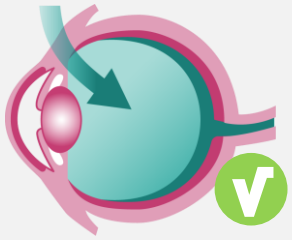
For IRD indications

ProQR inherited blindness platform

UNIQUE PLATFORM FOR PRECISION MEDICINE

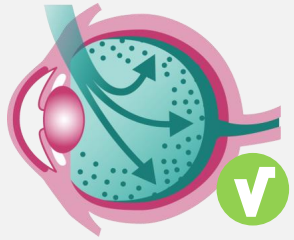
Targeted RNA oligo therapies

- RNA oligo designed to specifically address the mutations causing the disease
- >300 genetic eye diseases described



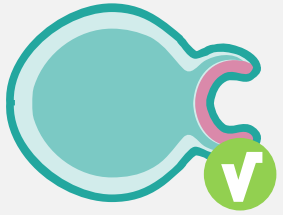
Intravitreal delivery is routine procedure

- Long half-life in the eye allows for dosing once or twice yearly
- Chemical modification enables naked delivery



Broad distribution allows for targeting of central and peripheral diseases

- Oligonucleotides distribute broadly to all different cell types
- Allowing for targeting central and peripheral disease

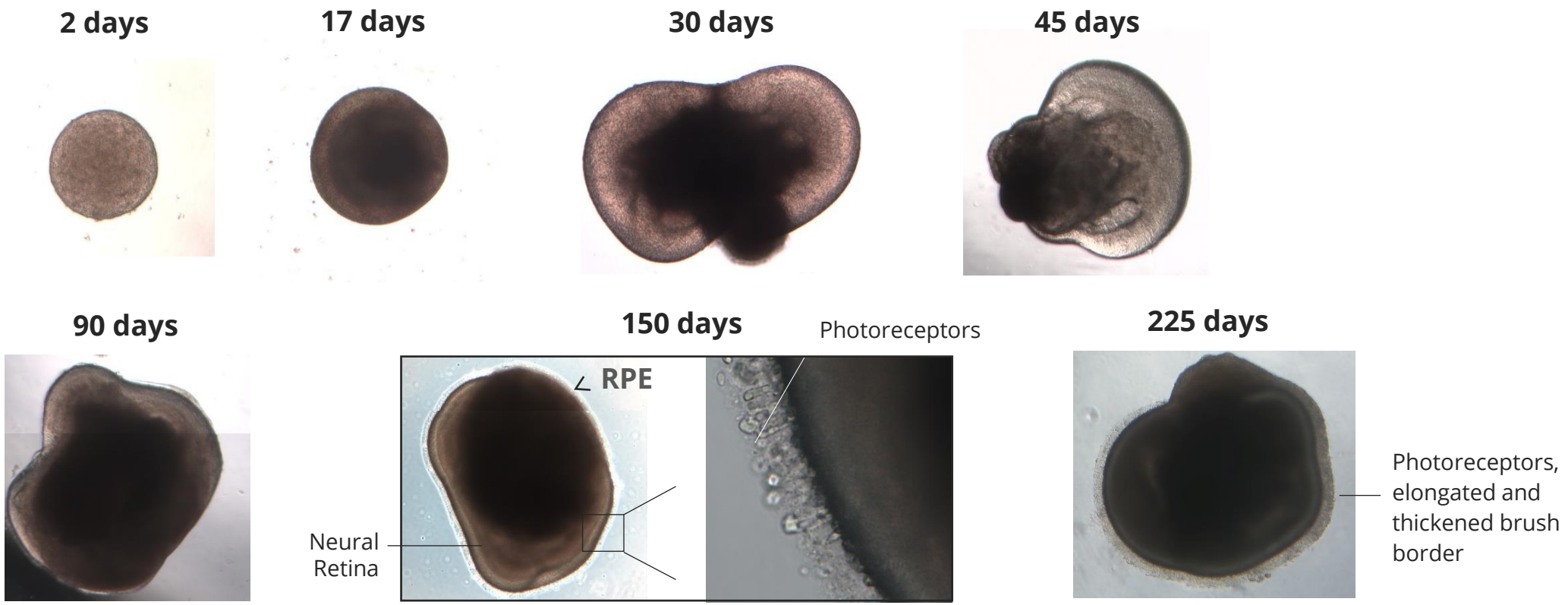


Predictive optic cup model

- Sophisticated organoid model for retinal dystrophies
- Accurately predicted in sepofarsen trial:
  - Clinically efficacious intravitreal dose level
  - Response to treatment
  - Time to onset of response

Human retinal organoids

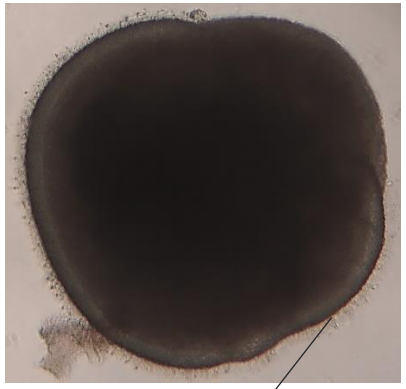
Differentiation from induced pluripotent stem cells (iPSC)



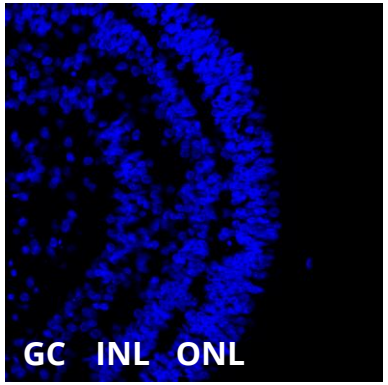
- Takes 150 days to generate organoids. After this they are ready treating with ASOs
- Retinal organoids can be wild-type (volunteer derived) or mutant (patient derived)

Human iPSC-derived retinal organoids

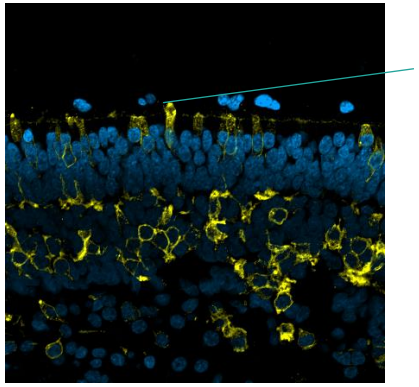
Brief introduction to the model



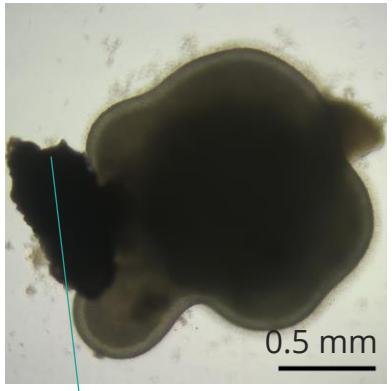
Photoreceptors



Cones

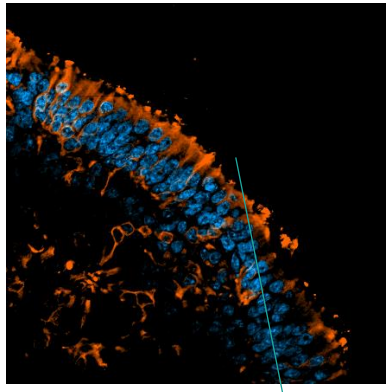


Opsin
red/green



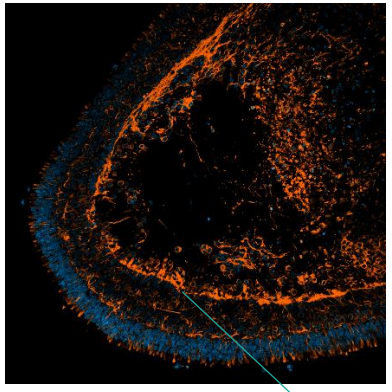
RPE

Rods



Rhodopsin

Ganglion Cells

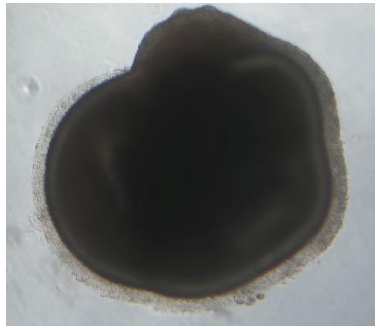


TuJ1

Substantial A-to-I editing in retinal organoids

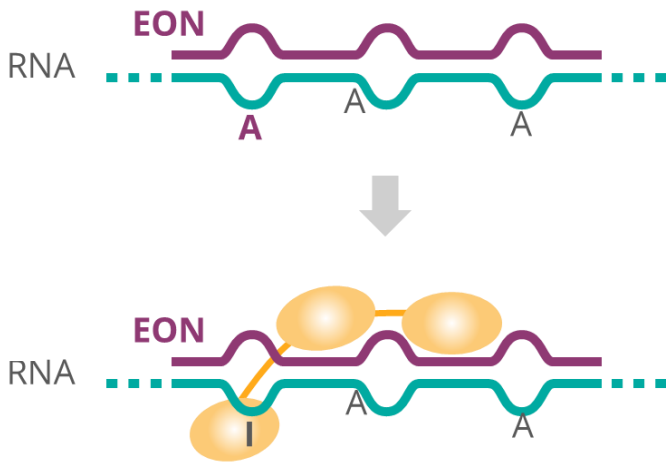
>40% editing was achieved in IPSC derived organoids

Retinal organoid

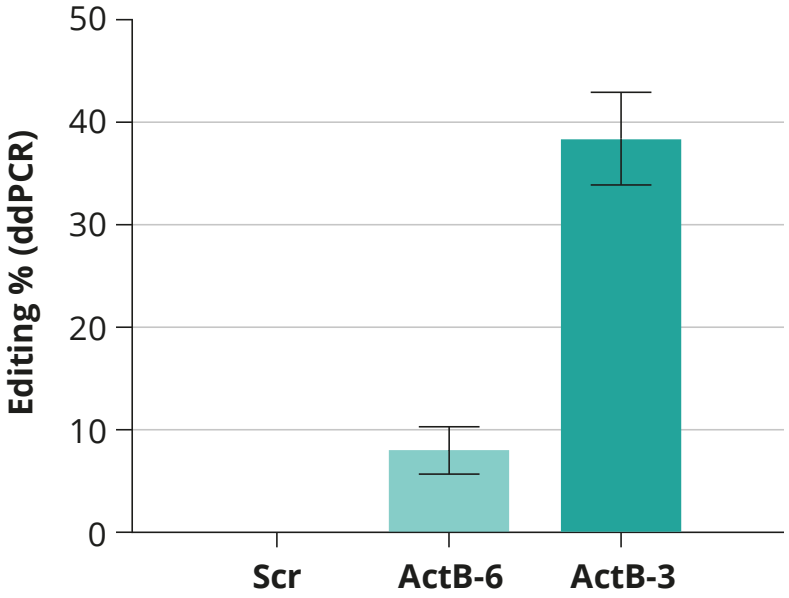


225 days

EON-directed therapeutic editing



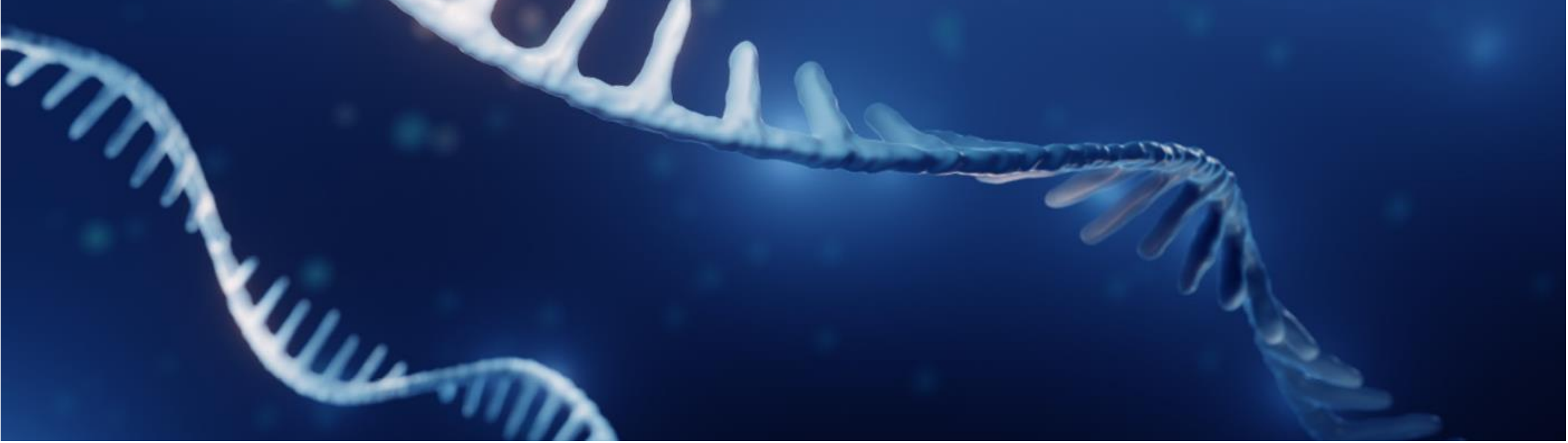
Editing of ACTB in human retinal organoids



- Each chemical modification improves EON editing efficacy
- The highest editing efficacy increase is obtained for EONs with all modification combined
- Over 40% editing was observed after gymnosis

Axiomer® is uniquely positioned in genetic medicines

- Axiomer® edits RNA using the body's own A-to-I editing machinery – no external enzymes have to be inserted into the cells
- Optimizing the EON designs and have shown excellent editing levels in retinal organoid models
- ProQR is developing Axiomer® for genetic eye disease
- ProQR will develop selected targets in genetic eye disease, and will provide further guidance on this in H2 2022



Trident®

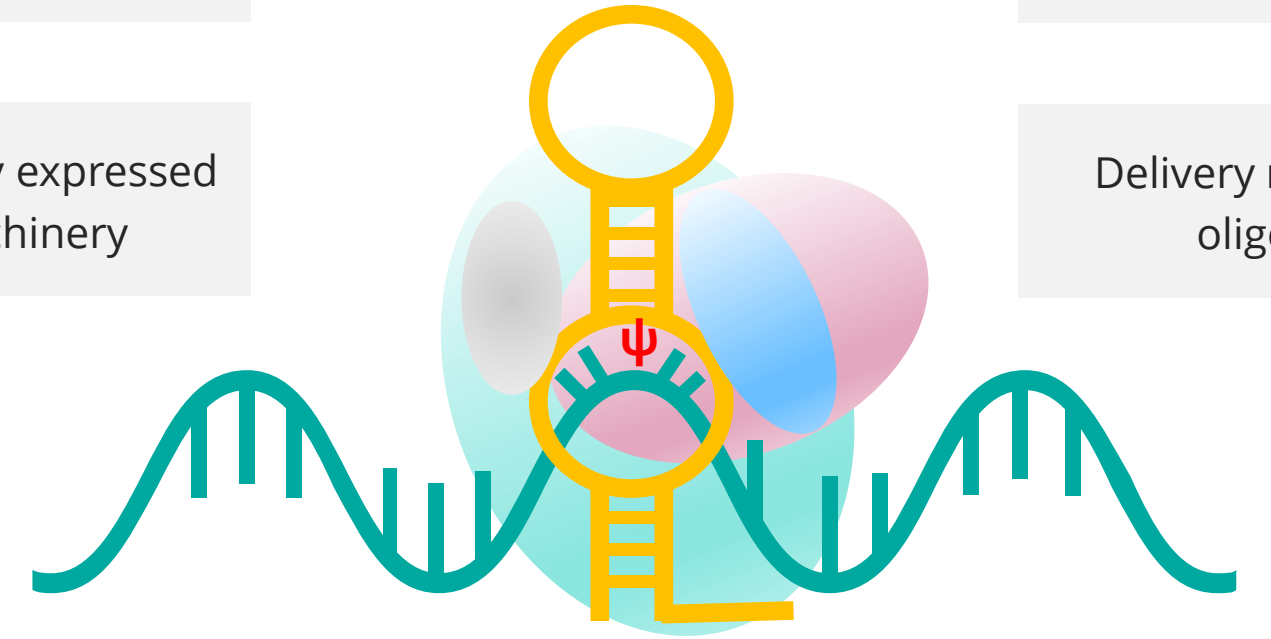
An emerging RNA Editing platform

Trident® RNA editing technology

Based on RNA-guided pseudouridylation of selected uridines in RNA

Translational read through and NMD inhibition

Use of endogenously expressed RNA editing machinery

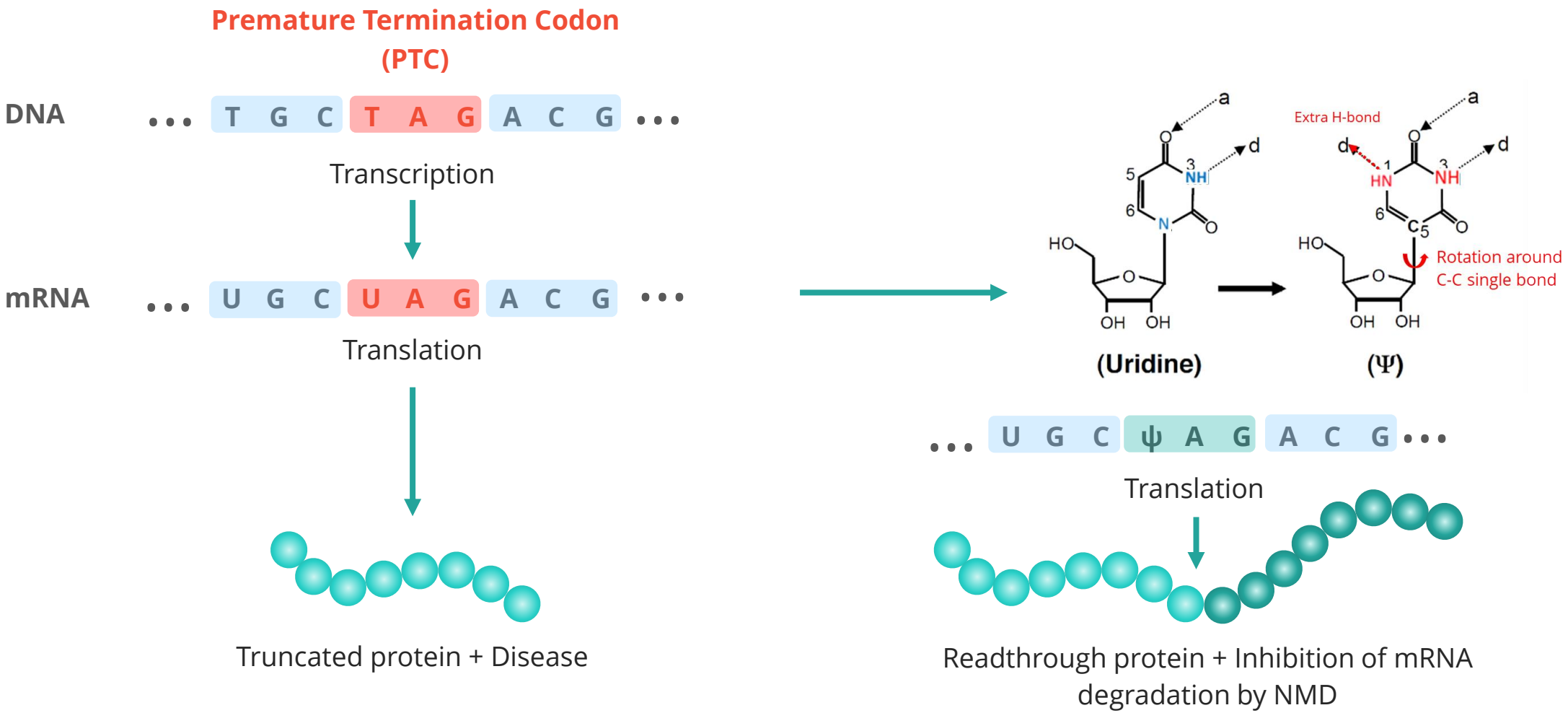


Site-specific PTC repair at the RNA level

Delivery modality: modified oligos or psEONS

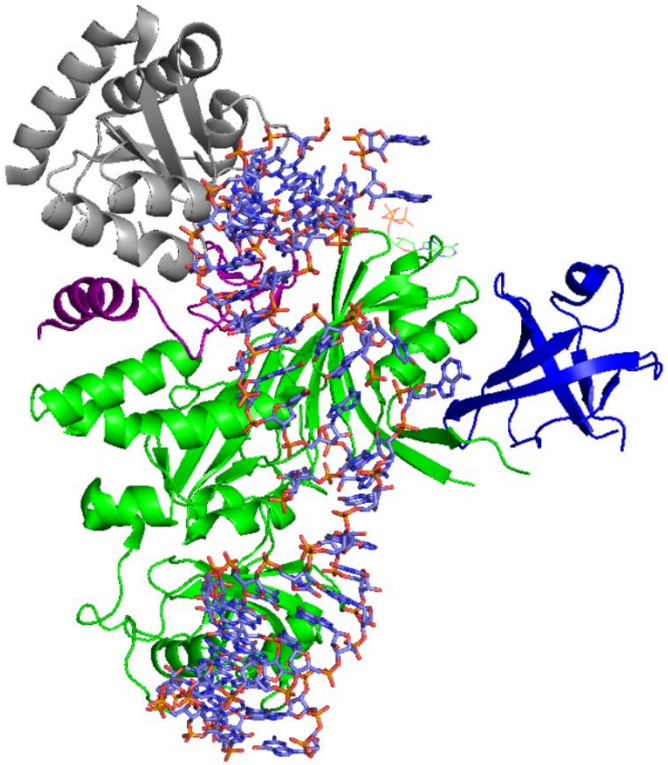
Targeted pseudouridylation of PTC in RNA

Translational read-through and nonsense mediated decay (NMD) inhibition



Optimizing guide-RNA design for therapeutic use

Computational modelling using Archaeal H/ACA box RNP



Archaeal H/ACA box RNP
(Li et al. 2006 Nature)

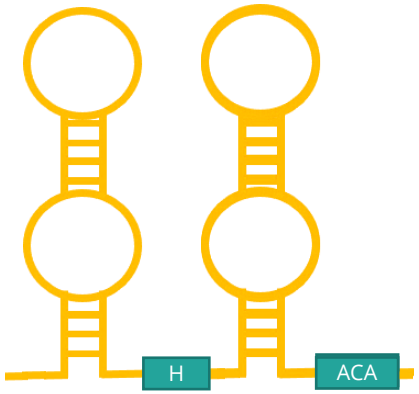
In silico, Biophysical, biochemical methods

Single hairpin guide with stems and loops reduced in size

gRNAs are halved and chemically modified

In silico and biochemical screening used to improve design (SAR)

Natural gRNAs: 130nt



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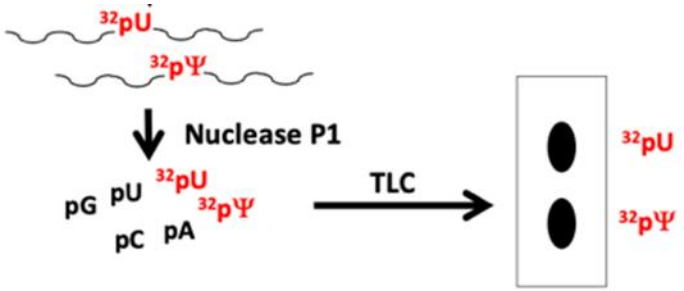
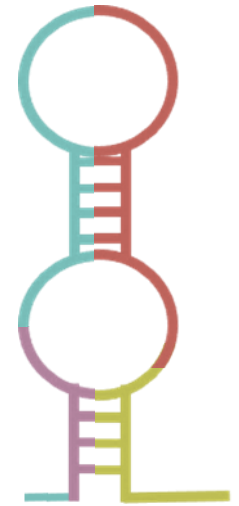
Pseudouridylation biochemical assay

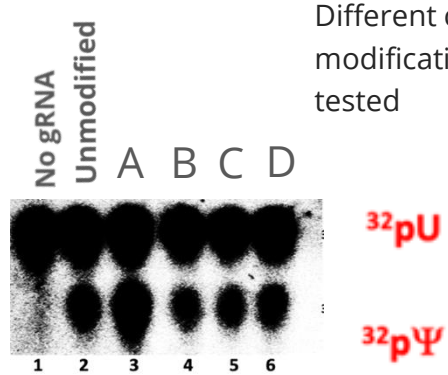


Single Hairpin

Modified gRNA



Different chemical modifications were tested



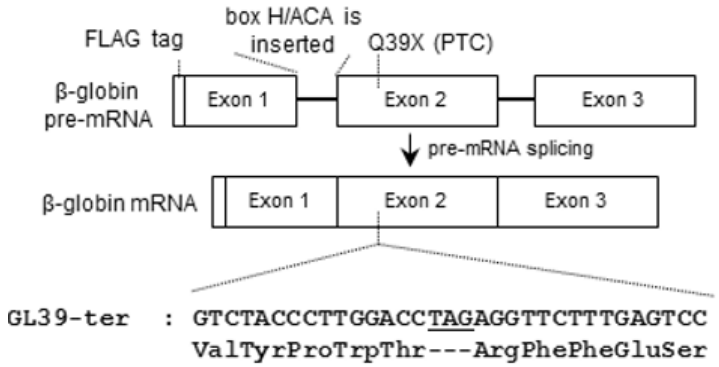
Example in beta-globin

- Trident® inhibits NMD (increases PTC-containing mRNA levels), which affects the NMD-sensitive beta-globin gene
- PTC insertion leads to decrease in beta-globin protein production
- One of the most common nonsense mutations in this gene is Q39X, prevalent in Mediterranean countries

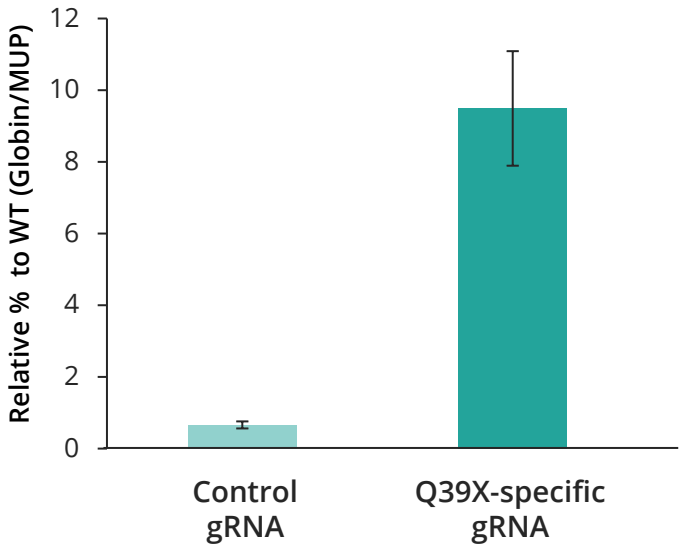
Trident®

Pseudouridylation PoC in human cells

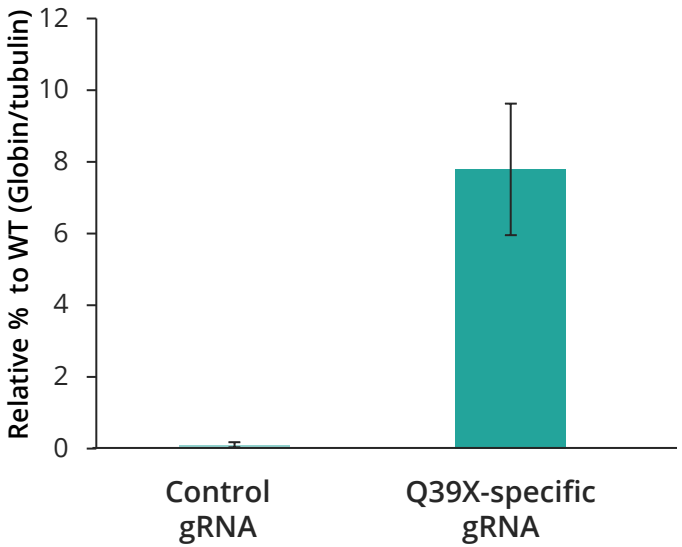
“Mediterranean” mutation



Increase of beta-globin mRNA



Increase of beta-globin protein



Sequence- and gRNA-specific readthrough and NMD-I effect

Trident® scientific progress summary

- The Trident® platform has numerous applications in mutation correction and protein modulation
  - 11% of genetic diseases are caused by premature termination codons (PTCs), in principle correctable with the technology
  - Specific amino acids can be altered to modulate protein function
- Achieved proof of concept in several models showing translational correction and inhibition of NMD
- Trident® technology can be applied as synthetic oligonucleotides or psEONs
- Further optimizations for development purposes are ongoing

Milestones

Recent achievements & anticipated milestones

Sepofarsen for *CEP290*-mediated LCA10

- ✓ Complete enrollment in pivotal Phase 2/3 *Illuminate* trial (January 2021)
- ✓ Start pediatric *Brighten* study (Q2 2021)
- Top-line readout from pivotal Phase 2/3 *Illuminate* trial in late Q1 / early Q2 2022

QR-421a for Usher syndrome and retinitis pigmentosa

- Start pivotal Phase 2/3 *Sirius* and *Celeste* trials by year end 2021
- Update from *Helia* extension trial by year end 2022

QR-1123 for autosomal dominant retinitis pigmentosa

- ✓ First clinical data in Q4 2021
- Repeated dosing study to start in 2022

QR-504a for Fuchs endothelial corneal dystrophy

- ✓ Trial open for enrollment (Q2 2021)
- First clinical data in 2022

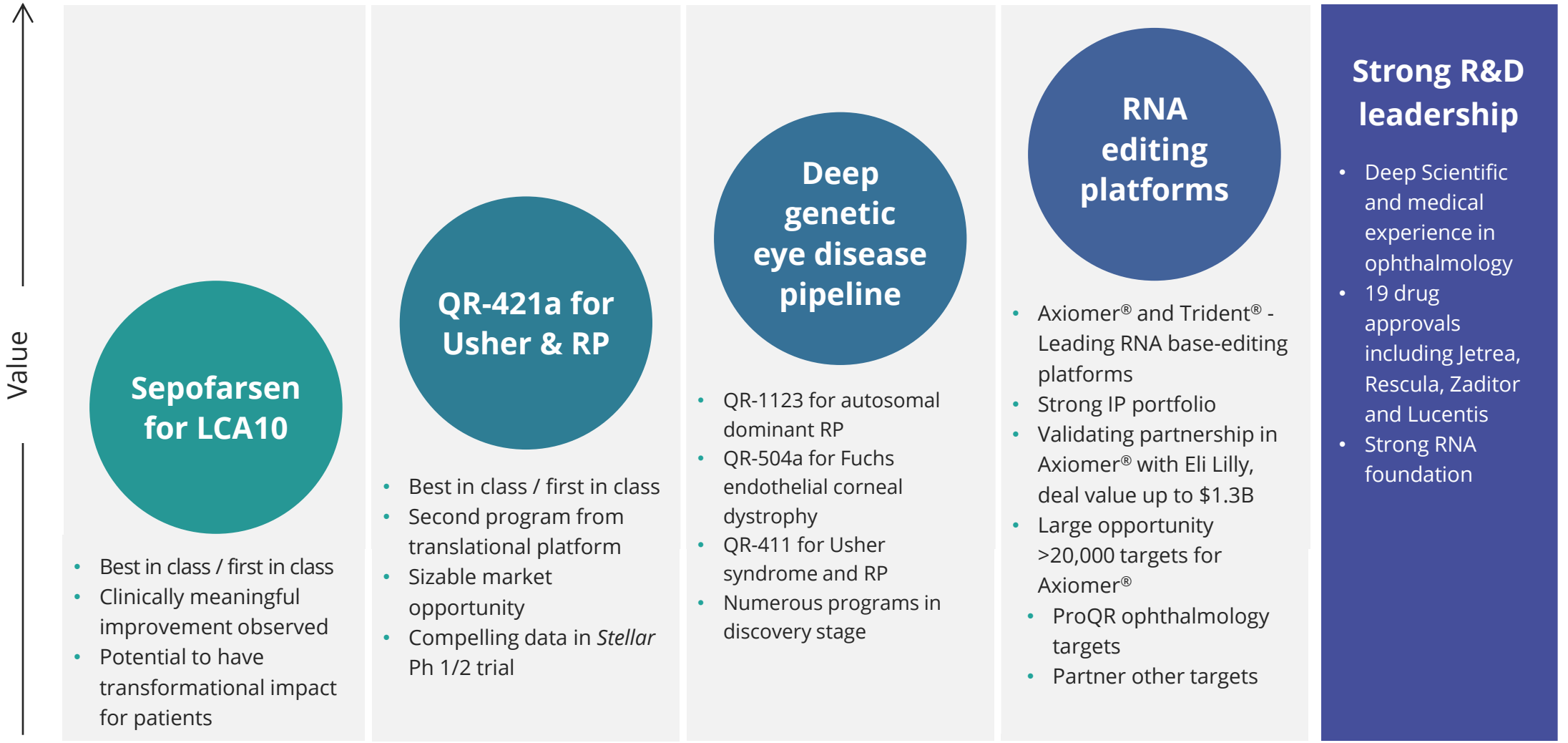
Axiomer® RNA editing platform technology

- Partnership with Lilly announced (September 2021) – up to 5 targets in liver and nervous system, $50 M
- ProQR will develop selected targets in genetic eye disease, and will provide further guidance on this in H2 2022

Additional genetic eye disease target

- Advance a target into pre-clinical development in 2022

The ProQR value proposition



ProQR®

IT'S IN OUR RNA