# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION

**Washington, D.C. 20549**

# FORM 6-K

**Report of Foreign Private Issuer**
**Pursuant to Rule 13a-16 or 15d-16 of**
**the Securities Exchange Act of 1934**

**For the month of April 2022**

**Commission File Number: 001-36622**

# PROQR THERAPEUTICS N.V.

**Zernikedreef 9**
**2333 CK Leiden**
**The Netherlands**
**Tel: +31 88 166 7000**
(Address, Including Zip Code, and Telephone Number,
Including Area Code, of Registrant's Principal Executive Offices)

Indicate by check mark whether the registrant files or will file annual reports under cover of Form 20-F or Form 40-F.

Form 20-F ☒ Form 40-F ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(1): ☐

Indicate by check mark if the registrant is submitting the Form 6-K in paper as permitted by Regulation S-T Rule 101(b)(7): ☐

On April 13, 2022, ProQR Therapeutics N.V. (the "Company") will host a webcasted conference call to provide an update on its sepofarsen program following a comprehensive post-hoc analysis of the data from the Phase 2/3 *Illuminate* trial and highlighted the Company's updated corporate strategy. A copy of the corporate presentation is attached hereto as Exhibit 99.1 and is incorporated herein by reference.

The Company hereby incorporates by reference the information contained herein into the Company's registration statements on Form F-3 (File No. 333-260775, File No. 333-260780 and File No. 333-248740).

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

**PROQR THERAPEUTICS N.V.**

Date: April 13, 2022

By: /s/ Smital Shah
Smital Shah
Chief Financial Officer

**INDEX TO EXHIBITS**

| Number | Description |
| --- | --- |
| 99.1 | Presentation for webcasted conference call. |

ProQR®

# STRATEGY UPDATE

Nasdaq: PRQR

Date: April 13, 2022

# Agenda

## Intro

**Sarah Kiely**
*Vice President Investor Relations and Corporate Communications*

## Presentation

**Daniel A. de Boer**
*Founder & CEO*

## Q&A

**Daniel A. de Boer**
*Founder & CEO*

**Smital Shah**
*Chief Business and Financial Officer*

**Aniz Girach, MD**
*Chief Medical Officer*

**Gerard Platenburg**
*Chief Innovation Officer*

# 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 updated strategic plans and intended benefits thereof, future operations, future preclinical and clinical trial plans and related timing of trials and results, regulatory pathway and design of preclinical and clinical trials (including sepofarsen and ultevursen), our planned interactions with regulatory authorities relating to our programs, statements about our research and development, the potential of our technologies and platforms, including Axiomer®, our current and planned partnerships with collaborators and the intended benefits thereof, 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 later data to alter initial and preliminary results of early-stage clinical trials, including as a result of differences in trial designs and protocols across different 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; the outcomes of our planned interactions with regulatory authorities; 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; our ability to maintain and service our loan facility with Pontifax and Kreos; 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.

# Two strategic pillars underpin our approach

*Operating at the intersection of RNA therapy and genetic eye diseases*

## Genetic eye diseases


## Axiomer® RNA editing technology

# Overview

- ***Illuminate* missed primary endpoint**
  - No critical trial conduct issues identified
- **Post-hoc *Illuminate* analysis completed**
  - Sepofarsen demonstrates efficacy signal consistent with earlier trials when comparing the active treatment and sham eyes to their corresponding contralateral eyes (CE)
- **CE preferred as a control with European Medicines Agency (EMA)**
  - EMA prospectively suggested given rare disease with heterogenous population vs. sham control
- **Next steps**
  - Engage with regulators to discuss *Illuminate* data in this context, along with ultevursen regulatory plan
  - Provide additional update Q3 or early Q4, depending on the timing of the regulatory meetings
- **Portfolio prioritization and restructuring initiatives**
  - Ultevursen – scale back to single Phase 2/3 *Sirius* tri with potential interim/futility analysis in 2023
  - Suspend further investment in QR-1123, QR-504a, and IRD research
  - Reduce workforce by approximately 30%, expected be effective in Q2
- **Accelerate Axiomer® RNA base-editing technology**
  - Discovered in 2014
  - Leading industry IP portfolio with 11 patent families
  - Lilly partnership
- **Strong cash position with runway into 2025**

# Sepofarsen

*RNA therapy for Leber congenital amaurosis 10*

# CEP290-mediated LCA10

CEP290-mediated LCA10 is an **ultra orphan disease**

One of the most aggressive forms of **inherited retinal blindness**

Patients lose most of their vision in **the first decade**

Disease biology well-understood for **genetic approaches**

Preclinical and early clinical data demonstrates **potential for sepofarsen** to impact quality-of-life for patients

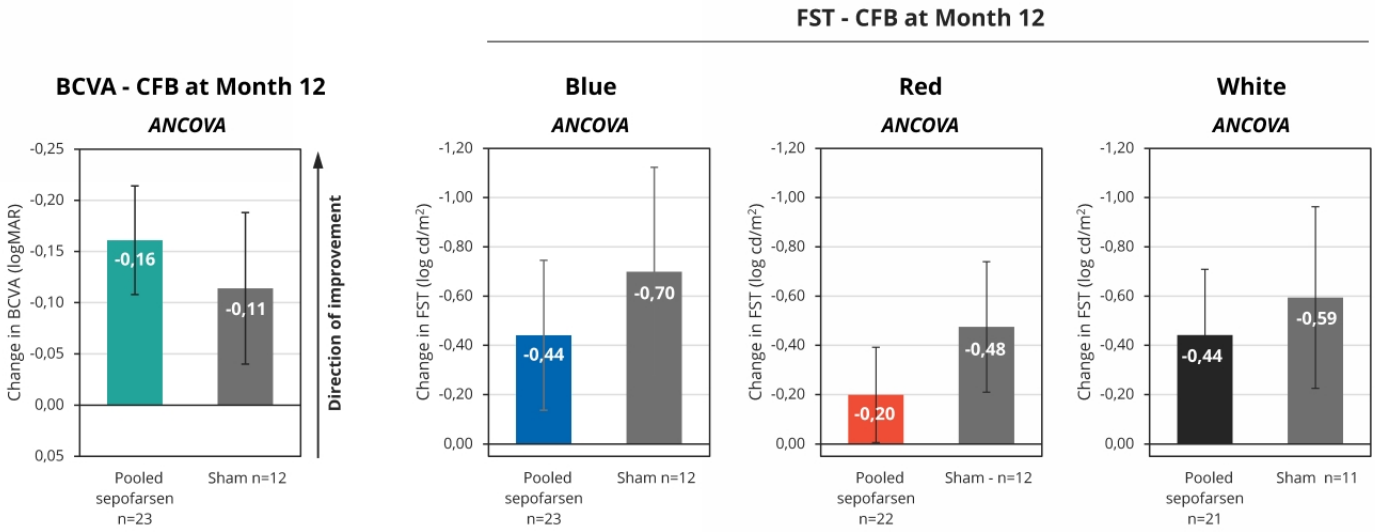
There are **no approved drugs** for LCA10

# *Illuminate* trial operational review

- All operational elements of *Illuminate* were reviewed
  - Included review of site-to-site variations, patient inclusion criteria, CMC aspects, clinical data analysis, among others
  - Removal of 1 patient in the post-hoc analyses (patient was at light perception at baseline) in the treatment group, resulting in n=23 for treatment groups and n=12 for sham
- No critical issues identified

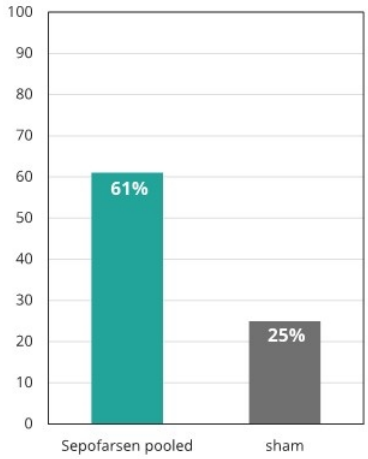
# Primary analysis

*Primary analysis of treated group vs parallel sham group showed no effect*

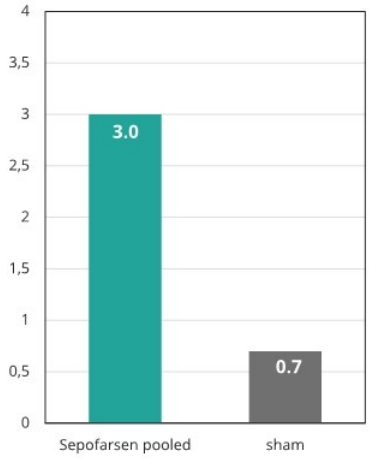


# Sepofarsen treated patients self-report an improvement in vision on 2 separate PROs

**PGI-C - % of subjects self-reporting an improvement CFB at Month 12**




**VFQ-25 – composite score CFB at Month 12**




**Single question PGI-C**

- 14/23 (61%) patients on sepofarsen self reported an improvement in their vision
- 3/12 (25%) of patients in sham reported an improvement in vision

**VFQ-25 composite score**

- Vision subscales indicated a more pronounced benefit in sepofarsen

PGI-C and VFQ-25 were pre specified analyses

**Investigator feedback**

*"Sepofarsen works, no question."*

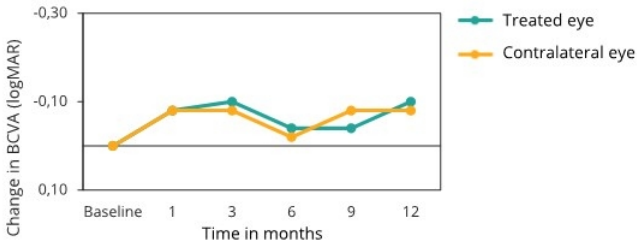
*"Patient is now able to see daughter's face in bright light conditions."*

*"Patient begged to have second eye treated."*

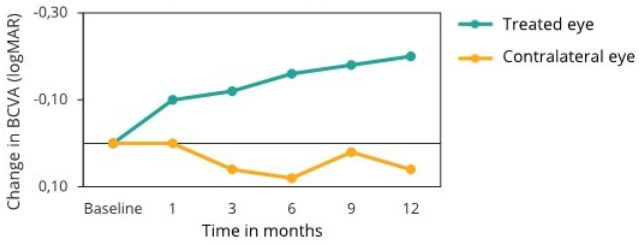
# Is sham the right control for small sample size trials?

- Significant visit-to-visit variability makes sham very noisy as a control in small sample size trials
  - Variability observed in sham eyes moves in parallel with each other in both eyes
- Using the difference between the treated eye (TE) and contralateral eye (CE) in the same patient corrects for this variability including
  - Day-to-day measurement variations intra-patient
  - Inter-patient phenotypic or baseline differences
- Due to above considerations EMA preferred CE as control for *Illuminate*
  - *Illuminate* protocol was harmonized globally for US FDA requirement of using sham

**Sham example:**
***Eyes behave the same***

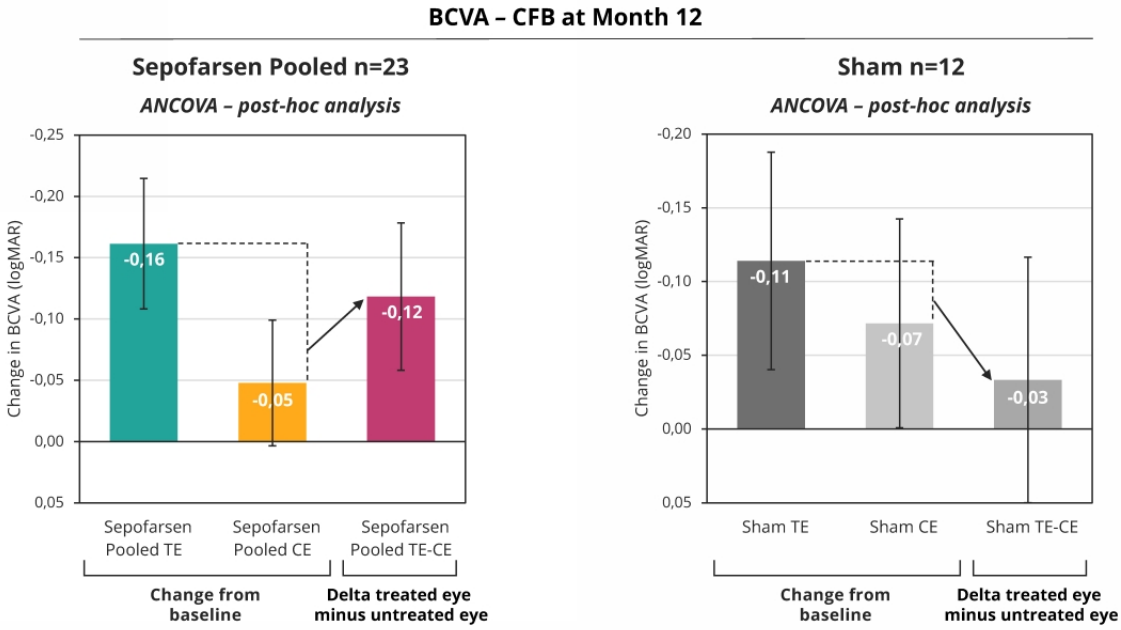



**Sepofarsen example:**
***Eyes behave different***



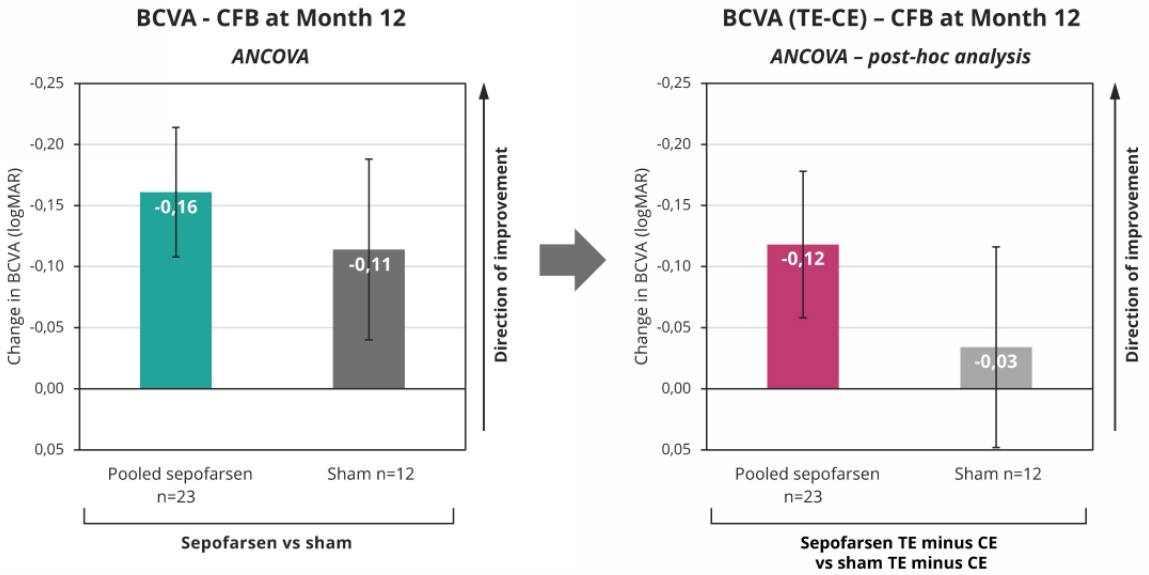
# Comparing to contralateral eye corrects for variability

*The "treated eye (TE) minus untreated eye (CE) analysis"*

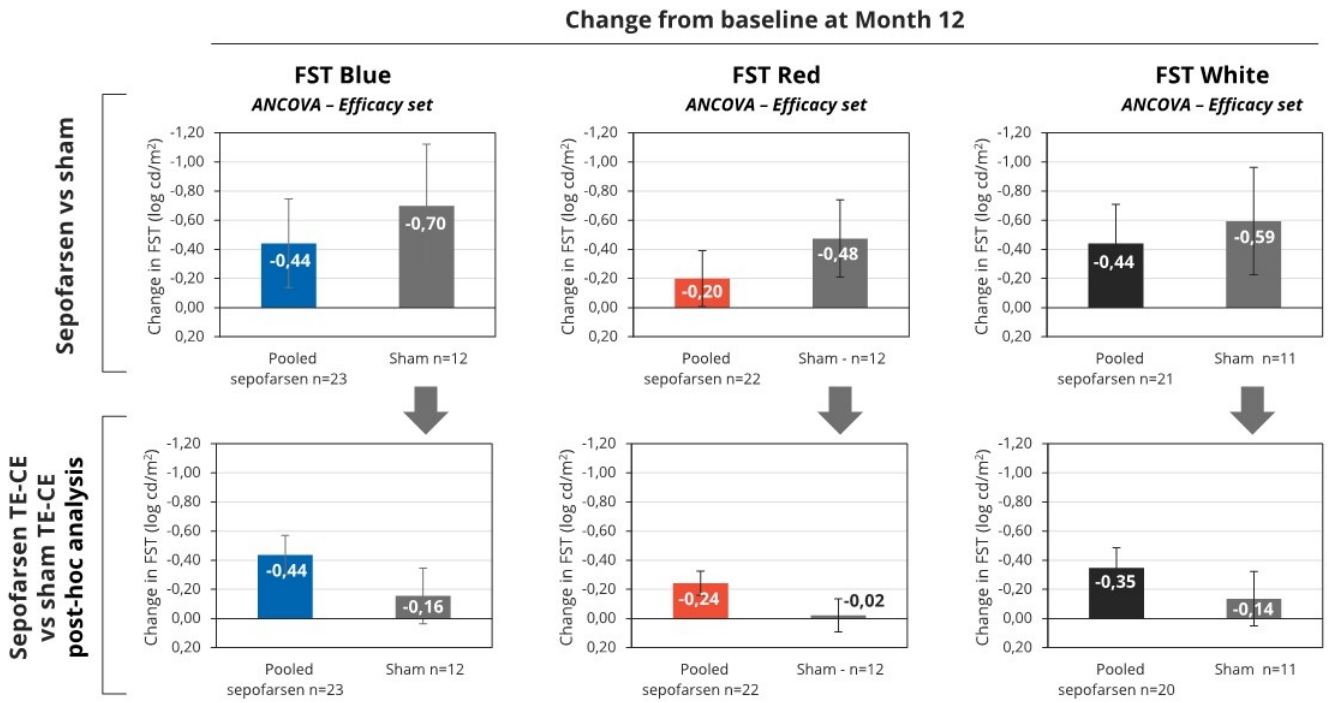


# BCVA at Month 12 post-hoc analysis

*No change in sham when TE is compared to sham CE*

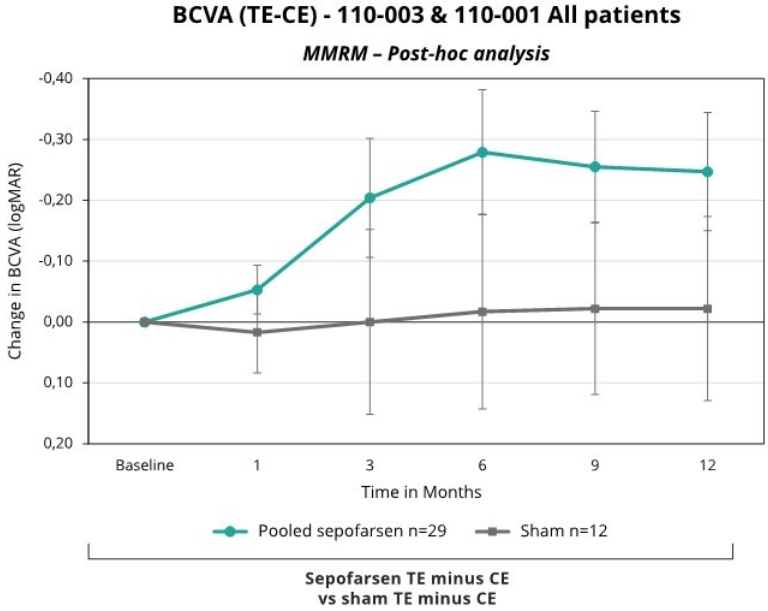


# FST - Comparing sham and contralateral eye as control



# Meta analysis - Combining Ph1/2 and Ph2/3 data

*BCVA TE-CE shows consistent and significant benefit compared to sham TE-CE*



# Sepofarsen next steps

- *Illuminate* results to be discussed with EMA and FDA in Q3
  - Evaluate next steps for program after regulatory feedback
  - Any further investment post Q3 (standalone or with a partner) subject to clear guidance from regulators
- Continuing the *Illuminate* and *Brighten* trials as recommended by the DSMC
  - Tolerability was observed to be similar to previous trials

# Learnings for IRD pipeline

**Scientific rationale for IRD platform remains sound**

- Evidence of benefit in post-hoc analysis of *Illuminate* is consistent with preclinical and early clinical data
- Dose levels predicted by preclinical data appear to demonstrate clinical activity
- Safety profile manageable across pipeline programs

**Development path learnings**

- Control differences exist (sham vs CE)
- Inter-patient variability limits ability to show mean level changes across different groups
- Analysis of sham group from both trials shows no consistent response when comparing TE to CE
- CE preferred by EMA regulators for both programs
  - Discussions with EMA to be conducted in Q3, followed by US FDA

# Ultevursen

*RNA therapy for retinitis pigmentosa and Usher syndrome*

# Ultevursen (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

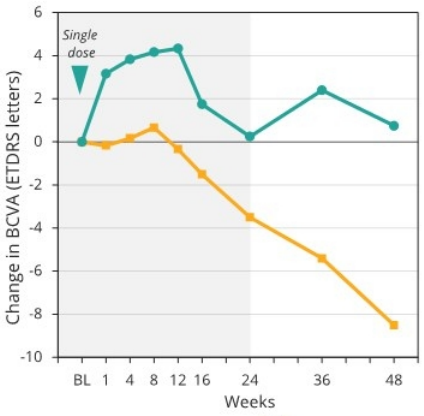
Potential first-in-class RNA therapy targeting ***USH2A* exon 13** mutations

- 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 tolerability

# Ultevursen Phase 1/2 *Stellar* trial results

*Concordant benefit in multiple endpoints*

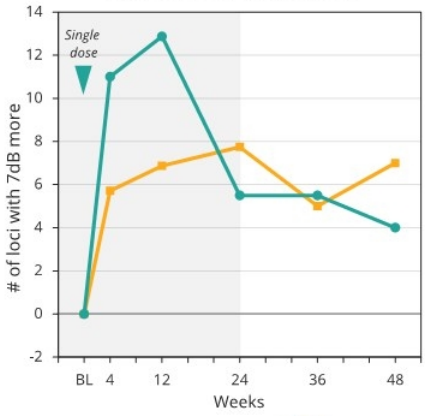
**Mean Change from Baseline in BCVA**
Advanced Population




**Phase 2/3 *Sirius* trial** SIRIUS

- Advanced population
- Primary endpoint BCVA

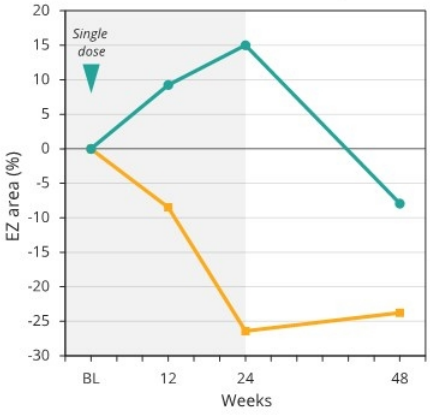
**Mean Number of retinal loci with ≥7dB improvement in static perimetry**
Early-moderate population




**Phase 2/3 *Celeste* trial** CELESTE

- Early to moderate population
- Primary endpoint static perimetry

**Ellipsoid zone area: % mean change from baseline**
All ultevursen treated subjects



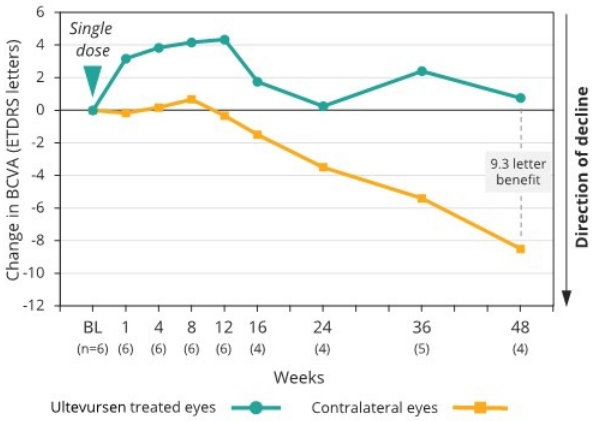

Ultevursen treated eye
Contralateral eye
Expected half-life of ultevursen

# BCVA stabilization driven by advanced population

*Mean change from baseline in BCVA after single injection*

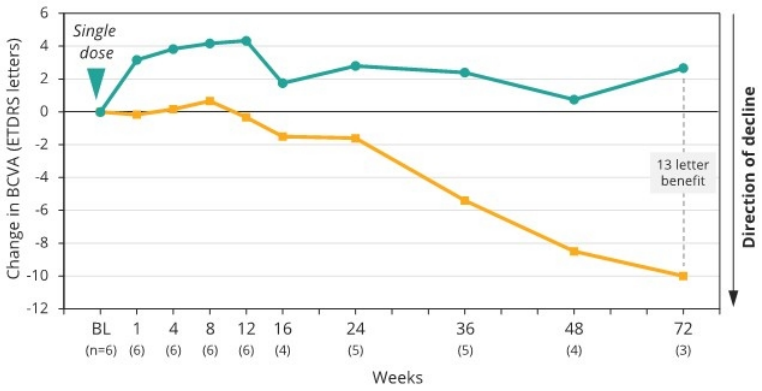
**Mean 9.3 letter benefit at week 48**

Advanced population (n=6)




**Mean 13 letter benefit at week 72**

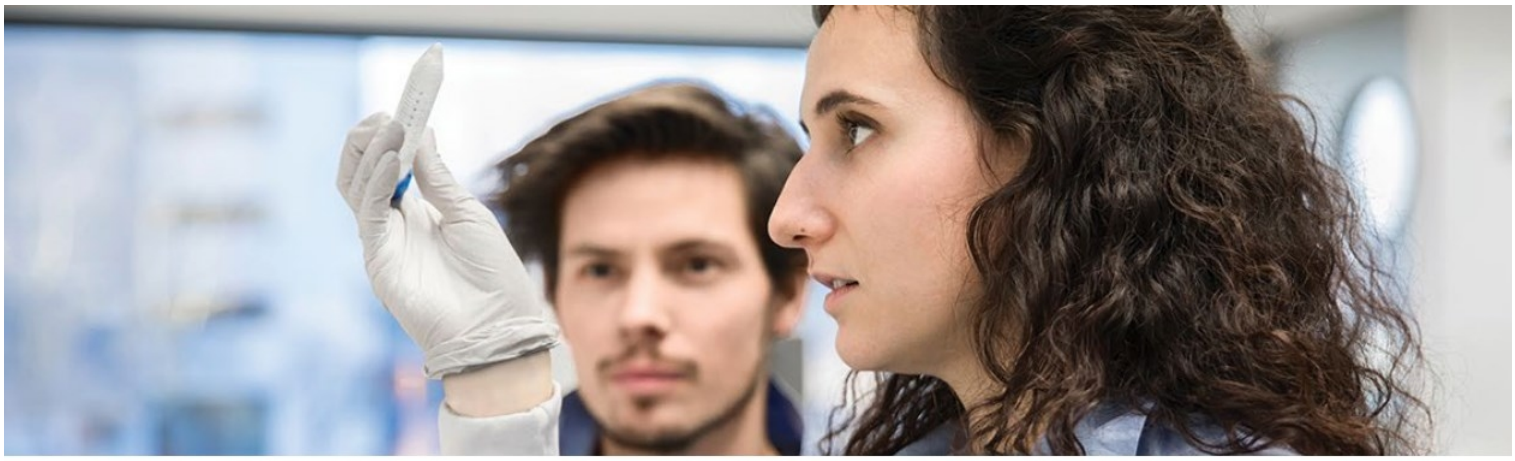
Advanced population (n=6)




- 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

# Ultevursen summary and next steps

- Ultevursen data continue to be robust; however clinical development can be optimized based on sepofarsen learnings
  - Single dose resulted in benefit for up to 72 weeks
  - Dose predicted preclinically observed to be active
  - Concordant response across multiple endpoints
- Ultevursen trials to be revised to mitigate development risk
  - Wind down *Celeste* trial to reduce investment
  - Revise *Sirius* trial to incorporate change in control from sham to CE
    - Discuss and seek alignment with regulators ahead of significant further investment (regulatory interaction planned in Q3)
    - Build in potential interim/futility analysis to mitigate investment risk with earlier data read out
- Objective to have primary readout well within cash runway



# Company Strategy Update

# Portfolio prioritization and restructuring initiatives

## Sepofarsen *for CEP290 mediated LCA10*

**Discuss** *Illuminate* post-hoc analyses with regulators in Q3

## Ultevursen *for USH2A mediated RP*

**Scale back** to a single Phase 2/3 *Sirius* trial with potential interim/futility analysis in 2023

## Suspend further investment

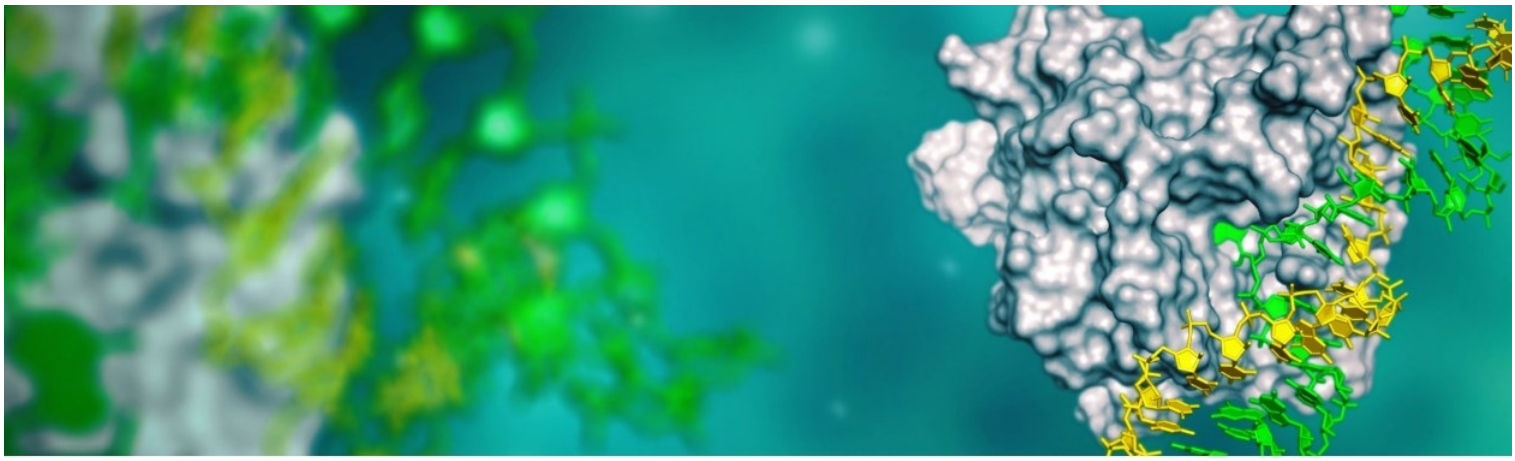
**QR-1123** *for P23H adRP*
**QR-504a** *for FECD3*
**IRD research**

## Workforce

**Reduce** workforce by 30%, expected to be effective in Q2

## Axiomer®

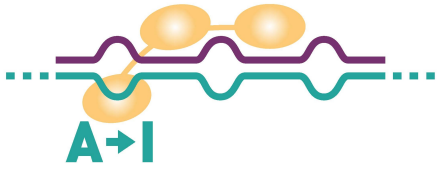
**Prioritize and accelerate** Axiomer® RNA editing platform technology, including the partnership with Lilly



# Axiomer®

*RNA base-editing platform technology*

# Axiomer® RNA base-editing platform technology




### Axiomer® A-to-I editing

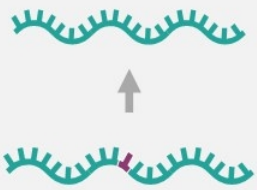
- Exploiting endogenous ADAR
- Recruited by synthetic Editing Oligonucleotide (EON)
- I is translated as a G, allowing to target G-to-A mutations
- Specific, potent, and stable by design
- >20,000 G-to-A mutations described in literature
- Approximately 60% editing efficiency achieved in cells and over 20% in retinal organoids

### Strong IP protection

- 11 patent families, 1 pending
- Foundational patents owned or exclusively licensed by ProQR
- Unrivaled know how on EON/psEON design and high-throughput assays
- Key collaborations with academic experts

# Repairing G-to-A Mutations

*Axiomer® has the potential to target broad range of diseases*



**Repairing G-to-A mutations**

- More than 20,000 G-to-A mutations described in literature

**>20,000 G>A mutations**

**Ophthalmology**
*>1,100 targets*

- Leber Congenital Amaurosis 4
- Usher syndrome
- Fuchs Endothelial Corneal Dystrophy
- Retinitis Pigmentosa type 3
- Stargardt Disease
- Primary Congenital Glaucoma

**Skin**

- Albinism
- Dystrophic Epidermolysis Bullosa
- Junctional Epidermolysis Bullosa
- Darier disease
- Epidermolysis Simplex

**CNS**

- Parkinson's Disease VIII
- Spinocerebellar Ataxia VII
- Alzheimer's Disease
- Huntington's Disease
- Pain disorders

**Lung**

- Cystic Fibrosis
- Primary ciliary dyskinesia
- Surfactant Metabolism Dysfunction
- ABCA3 deficiency
- Familial Pulmonary Fibrosis

**Kidney**

- Polycystic kidney disease

**Oncology**

- KRAS driven tumors
- P53 driven tumors

**Blood / Cardiovascular system**

- Beta thalassemia
- Alpha thalassemia
- Progeria

**Liver**

- Alpha-1 Antitrypsin Deficiency
- Hurler Syndrome
- Factor V Deficiency
- Transthyretin-related hereditary amyloidosis
- Wilson disease
- Hereditary Hemochromatosis
- Ornithine Transcarbamylase deficiency
- Hemophilia B
- Pompe Disease

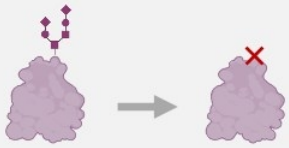
*And many more...*

# Axiomer® - beyond mutation repair

*Site-specific protein engineering & Post-translational modifications*

**Alter phosphorylation sites**

Targeting of **phosphorylation** sites (activity switches) to regulate protein activity



**Alter glycosylation sites**

- Targeting of **glycosylation** sites changes localization, folding and protein function
- Prevent immune escape of **glycosylated** tumor antigens

**Alter ubiquitination sites**

Changing a **ubiquitination** site slows down protein degradation (to treat haplo-insufficiencies)

**Potential to edit more than 400 different types of PTMs**

- Proteolytic cleavage
- Autocleavage
- Acetylation
- SUMOylation

# Axiomer® partnering strategy

**ProQR will maintain all global exclusive rights to the >1,100 genetic eye disease targets of Axiomer®**

- ProQR will develop selected targets in ophthalmology
- The initial batch of genetic eye disease targets that ProQR will advance into the pipeline will be announced in the next 12 months

**Up to 5 targets in liver and nervous system are licensed exclusively to Lilly**

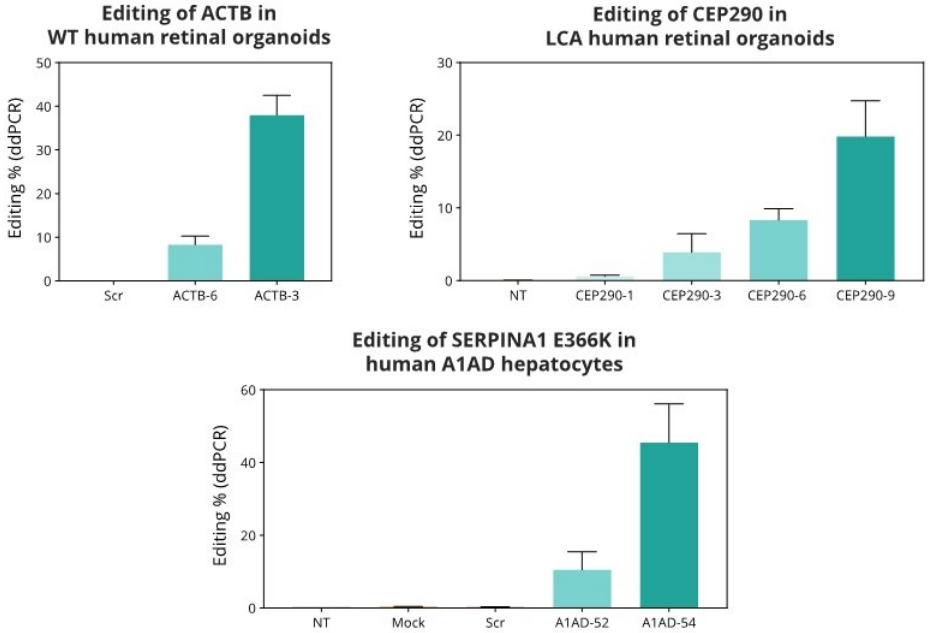

**Remainder of the targets remain unencumbered with strong potential for further value creation through additional partnerships**

# Axiomer® therapeutic applications

*IRD, liver, CNS and beyond*

# Substantial A-to-I editing in multiple models

*Potential to go after retina, liver and CNS targets*




**Retina**

- Over 40% editing in patient derived retinal organoids and over 20% editing observed for CEP290

**Liver**

- Up to 50% editing achieved in liver cell model
- Alpha-1 antitrypsin deficiency (A1AD) affects the liver and lung

**CNS**

- Approximately 60% editing achieved in CNS cell model (data not shown)

# Axiomer® patent protection beyond 2040

| Docket | Priority | Feature | Status |
|---|---|---|---|
| 0004 | 17 Dec 2014 | Targeted RNA Editing using endogenous ADARs | Granted EP US JP RU ZA |
| 0013 | 22 Jun 2016 | 'Single stranded' EONs | Granted US on 27APR21 |
| 0014 | 01 Sep 2016 | Chemically modified EONs | Granted EP US |
| 0016 | 19 Jan 2017 | EONs + protecting SONs | Published |
| 0020 | 14 Feb 2018 | EONs with ribose (e.g. 2'-MOE) modifications | Published |
| 0023 | 18 May 2018 | • EONs with phosphorothioate linkages,<br>• EONs with chiral linkages (e.g. PS, PN) | Published |
| 0026 | 11 Feb 2019 | • EONs with UNA modifications<br>• EONs with phosphonacetate linkages | Published |
| 0029 | 03 Apr 2019 | EONs with methylphosponate linkages | Published |
| 0031 | 24 Apr 2019 | Targeted editing inhibition | Published |
| 0032 | 13 Jun 2019 | EONs with base modifications for increased catalytic activity | Published |
| 0039 | 23 Jul 2020 | Undisclosed | Unpublished |

# Next steps Axiomer® platform

**In house strategy**

- Expand investments in Axiomer® platform and pipeline development and target selection activities
- Expect to present further non-clinical data updates throughout 2022
- Planning to announce internal development targets in H2 2022
  - Develop *in vivo* PoC in multiple programs with initial focus on Liver, CNS and ophthalmology
  - First IND expected in 18-24 months
  - Development of additional Therapeutic Areas in parallel

**Partnership strategy**

- Continue to execute on the partnership with Lilly
- Potential for additional partnerships, building on industry leading IP estate and strong development capabilities

# Summary

# Strategic priorities and milestones

## Strategic priorities

- **Genetic eye disease**
  Explore regulatory path for ophthalmology based on comparing active treatment and sham eyes versus their corresponding contralateral eye with EMA and FDA; subject to regulatory feedback develop select IRD programs
- **RNA editing technology**
  Accelerate development of the Axiomer® platform, including initial focus on liver, CNS, and ophthalmology

## Milestones

**IRD pipeline - sepofarsen and ultevursen**

- Meet with EMA and FDA to discuss *Illuminate* results Q3
- Provide regulatory update Q3 or early Q4, depending on timing of regulatory meetings
- Ultevursen *Helia* extension trial update by year end 2022
- Ultevursen *Sirius* Phase 2/3 potential interim/futility analysis in 2023

**Axiomer® RNA editing platform technology**

- Partnership with Lilly announced (September 2021) – up to 5 targets in liver and nervous system, $50 million
- Announce internal targets and provide further pipeline guidance in H2 2022

**Cash position/runway**

- YE 2021: €187.5 million
- Runway into 2025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