Phase 1b/2 interim results of QR-421a RNA therapy in retinitis pigmentosa due to mutations in the *USH2A* gene (*Stellar* trial)

David G. Birch[1], Isabelle Audo[2,3,4], K. Thiran Jayasundera[5], Isabelle Meunier[6,7], Rachel M. Huckfeldt[8], Robert K. Koenekoop[9,10], Paul Yang[11], Ellen C. Dahler[12], Eduard P. M. de Cock[12], John Taylor[13], Naveed K. Shams[12], Aniz Girach[12]

[1]Retina Foundation of the Southwest, Dallas, TX, USA; [2]Sorbonne Université, INSERM, CNRS, Institut de la vision, Paris, France; [3]CHNO des Quinze-Vingts, DHU Sight Restore, INSERM-DGOS CIC 1423, Paris, France; [4]Institute of Ophthalmology, University College of London, London, London, UK; [5]Department of Ophthalmology and Visual Sciences, W. K. Kellogg Eye Center, University of Michigan, Ann Arbor, MI, USA; [6]Institute for Neurosciences of Montpellier, INSERM, Montpellier University, Montpellier, France; [7]National Reference Centre for Inherited Sensory Diseases, Montpellier University, CHU, Montpellier, France; [8]Department of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA, USA; [9]Department of Pediatric Surgery, Montreal Children's Hospital, McGill University and McGill University Health Centre Research Institute, Montreal, QC, Canada; [10]Department of Human Genetics and Ophthalmology, Montreal Children's Hospital, McGill University and McGill University Health Centre Research Institute, Montreal, QC, Canada; [11]Casey Eye Institute, Oregon Health & Science University, Portland, OR, USA; [12]ProQR Therapeutics, Leiden, Netherlands; [13]YBR Analytics, Jacksonville, FL, USA.

This study was sponsored by ProQR Therapeutics.

Disclosures: DGB reports grant funding from ProQR Therapeutics during the conduct of the study.

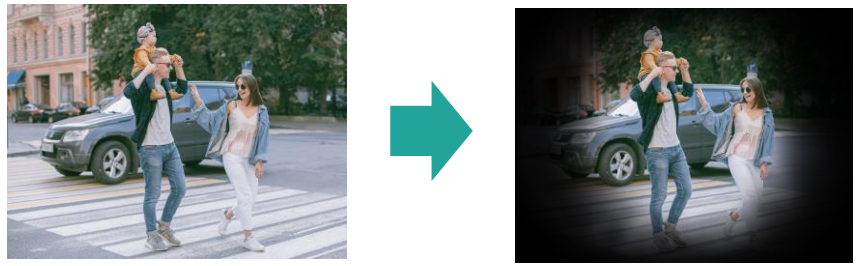
Presented at the European Society of Retina Specialists (EURETINA) Virtual Meeting, September 9–12, 2021

Introduction

- Retinitis pigmentosa (RP) is a group of inherited retinal diseases causing progressive blindness

Early–moderate disease

Losing visual field from the outside-inward



Advanced disease

Losing visual acuity (VA)

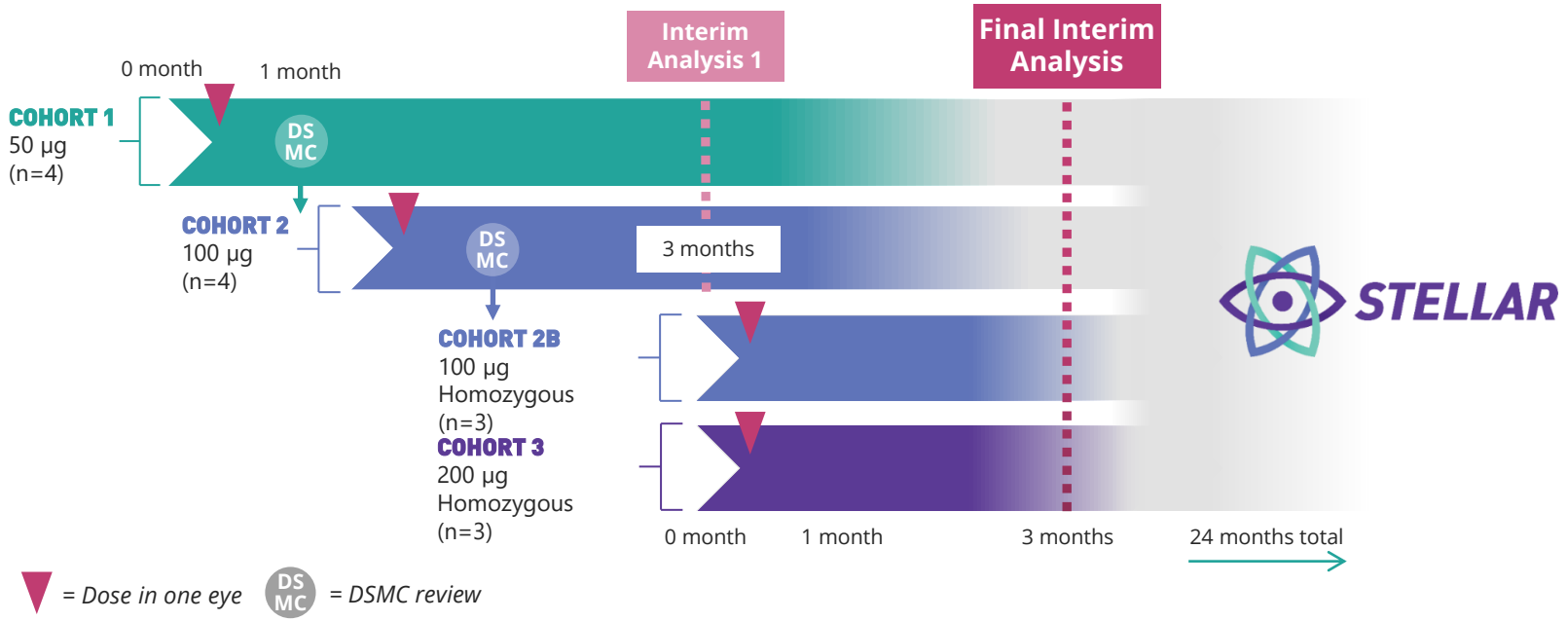
- *USH2A* gene mutations are the most common cause of autosomal recessive RP (arRP)[1]
- Exon 13 mutations in the *USH2A* gene are present in non-syndromic RP (nsRP) and in a syndromic form of RP called Usher syndrome type 2, the leading cause of deaf-blindness[2,3]
- To date, there are no approved treatments for the vision loss associated with mutations in *USH2A* gene

The *Stellar* trial evaluates the safety and tolerability of QR-421a, an RNA antisense oligonucleotide, in individuals with biallelic mutations in exon 13 of *USH2A*

1. Verbakel S et al. Prog Retin Eye Res. 2018;66:157–186. 2. Rivolta C et al. Am J Hum Genet. 2000;66:1975–1978. 3. McGee TL et al. J Med Genet. 2010; 47(7):499–506

Stellar trial overview

- **Study design**: 24-month, multicenter, Phase 1b/2 dose-escalation single-dose study
- **Participants**: Aged ≥18 years with arRP and homozygous or compound heterozygous *USH2A* exon 13 mutations
- **Treatment**: Single intravitreal QR-421a injection (50 µg, 100 µg or 200 µg) or sham injection
- **Primary endpoint**: Frequency and severity of adverse events
- **Secondary endpoints**: Change in functional and structural outcome measures and serum pharmacokinetics



Fourteen participants received QR-421a (4 received the 50 µg dose, 7 received the 100 µg dose and 3 received the 200 µg dose) and 6 participants received sham.

arRP, autosomal recessive retinitis pigmentosa; DSMC, data and safety monitoring committee

QR-421a was well tolerated at all doses

- QR-421a was well tolerated in **>3,700** subject follow up days
- No serious adverse events or inflammation were observed
- One participant had worsening of pre-existing cataracts that was deemed not treatment related by the investigator
- Progression of pre-existing cystoid macular edema was observed in one participant, that is being managed with standard of care

Most common treatment emergent ocular adverse events (>10%)

	QR-421a		Sham	
	TE (n=14)	**UE (n=14)**	**TE (n=6)**	**UE (n=6)**
Eye pain	3 (**21.4%**)	1 (7.1%)	1 (**16.7%**)	0 (0.0%)
Lacrimal increase	3 (**21.4%**)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Anterior chamber cells	2 (**14.3%**)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Conjunctival haemorrhage	2 (**14.3%**)	0 (0.0%)	2 (**33.3%**)	0 (0.0%)
Vision blurred	2 (**14.3%**)	1 (7.1%)	1 (**16.7%**)	1 (**16.7%**)
Intraocular pressure increased	2 (**14.3%**)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Injury, poising and procedural complications	2 (**14.3%**)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Conjunctival hyperaemia	1 (7.1%)	0 (0.0%)	1 (**16.7%**)	0 (0.0%)
Eye pruritus	1 (7.1%)	0 (0.0%)	1 (**16.7%**)	0 (0.0%)
Visual impairment	1 (7.1%)	1 (7.1%)	1 (**16.7%**)	1 (**16.7%**)
Corneal opacity	0 (0.0%)	0 (0.0%)	1 (**16.7%**)	0 (0.0%)
Foreign body sensation	0 (0.0%)	0 (0.0%)	1 (**16.7%**)	0 (0.0%)
Maculopathy	0 (0.0%)	0 (0.0%)	1 (**16.7%**)	1 (**16.7%**)
Photopsia	0 (0.0%)	1 (7.1%)	1 (**16.7%**)	1 (**16.7%**)
Vitreous detachment	0 (0.0%)	0 (0.0%)	1 (**16.7%**)	0 (0.0%)

TE, treated eyes; UE, untreated eyes

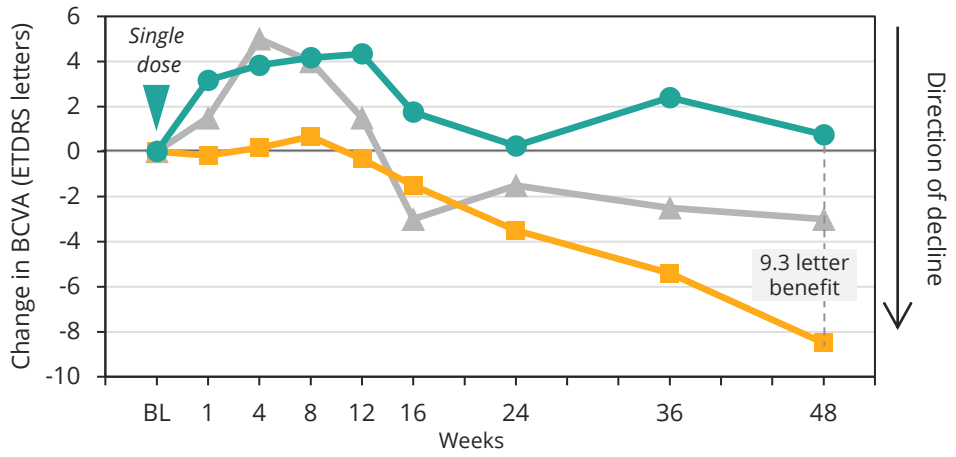
Benefits in BCVA and static perimetry following single injection QR-421a treatment

- BCVA stabilization was observed in QR-421a-treated eyes, versus decline observed in untreated eyes
- At week 48, mean BCVA benefit was **6.0 letters** for all QR-421a-treated participants
- **Results were driven by advanced disease stage patients**
  - Mean BCVA benefit was **9.3 letters** in advanced stage participants (n=6)
- No BCVA benefit was observed in sham-treated eyes

- Mean change from baseline in number of loci with improved static perimetry was **9.2 versus 6.1 loci** in QR-421a-treated eyes versus untreated eyes at week 12
- **Results were driven by early–moderate stage patients**
  - Mean change of **12.9 versus 6.9 loci** in QR-421a-treated eyes versus untreated eyes
- Sham-treated eyes responded similarly to QR-421a-untreated eyes

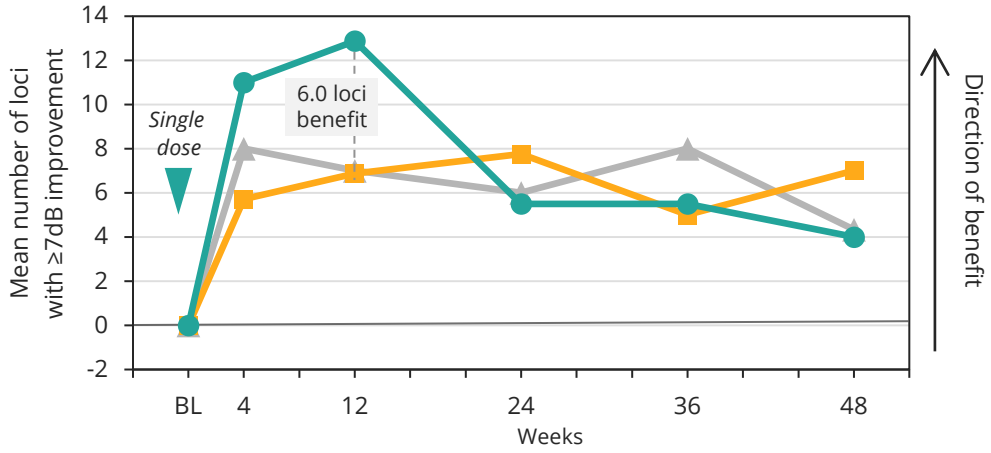
Mean Change from Baseline in BCVA

Advanced Population



Mean Number of retinal loci with ≥7dB improvement in static perimetry

Early-moderate population

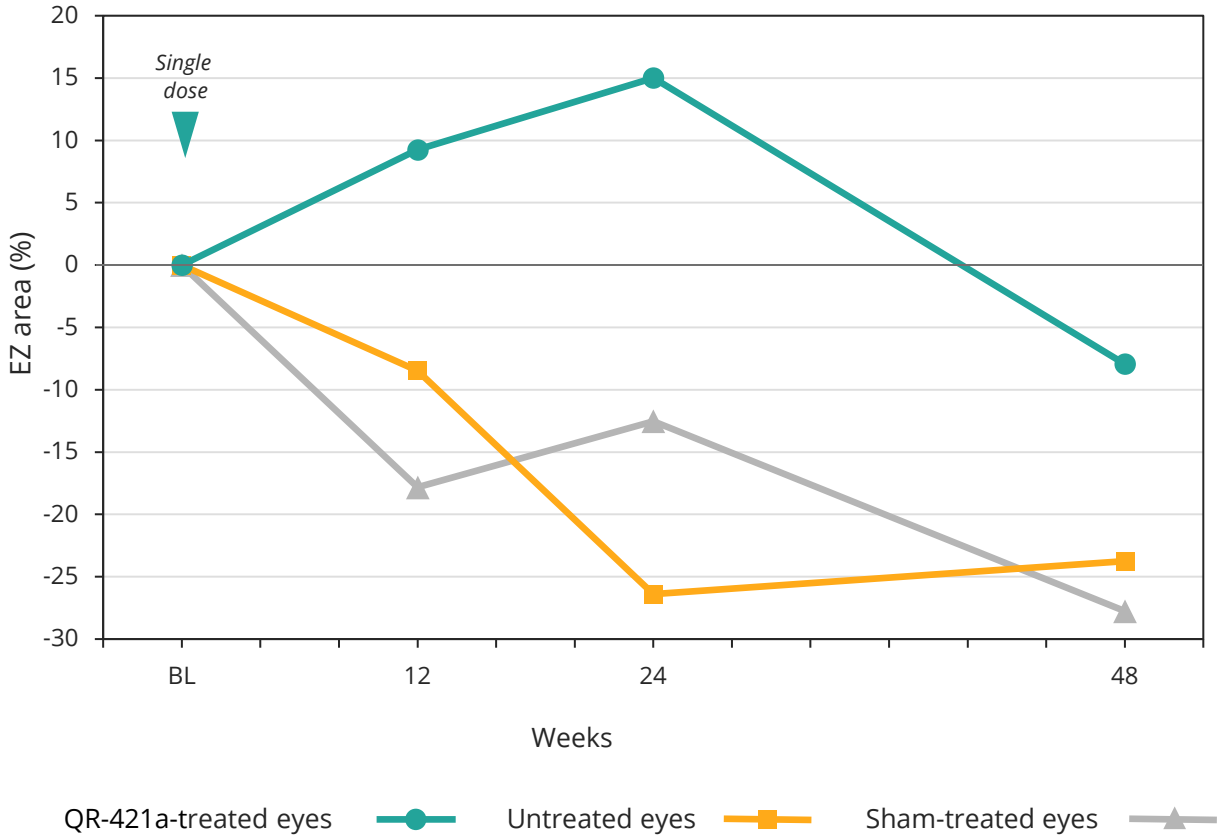


BCVA, best-corrected visual acuity; loci, locations

QR-421a Treated eyes — Untreated eyes — Sham Treated eyes

Stabilization of retinal structure in QR-421a treated eyes following single injection

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



- Mean change from baseline in the EZ-area, measured by OCT in the central macular area, at week 24:
  - **+15.0%** in QR-421a-treated eyes
  - **–26.4%** in untreated eyes
  - **–12.5%** in sham-treated eyes
- Stabilization of the retinal structure in QR-421a-treated eyes out to 48 weeks, after single dose
- Deterioration of the retinal structure in untreated and sham-treated eyes in line with natural history

OCT, optical coherence tomography

Conclusions

- QR-421a was well tolerated at all doses in participants with exon 13 mutations in *USH2A*
- QR-421a demonstrated encouraging evidence of visual acuity stabilization and clinically significant improvements in retinal sensitivity, that is supported by objective retinal structural imaging data, after a single dose
- Improvement in BCVA was driven by the advanced disease stage population, whereas improvement in static perimetry was driven by the early–moderate disease stage population
- *Helia,* an open-label extension trial, has been planned to follow up the *Stellar* trial participants, and 2 Phase 2/3 randomized, double-masked, multiple dose trials have been also planned:

Name	Stage	Population	Primary endpoint
Sirius	Phase 3	Advanced	BCVA
Celeste	Phase 3	Early–moderate	Static perimetry

Thank you to all *Stellar* participants and investigators

If you would like further information, please contact:

David G. Birch
dbirch@retinafoundation.org

Disclosures

DGB, **IA, KTJ**, **IM**, **RKK**, **RMH**, and **PY** report grant funding from ProQR Therapeutics during the conduct of the study.

ECD, **EPMC**, **NKS**, and **AG** are employees of ProQR Therapeutics.

JT is a former employee of ProQR Therapeutics.

Acknowledgements

The Stellar study was funded by ProQR Therapeutics, supported by the Foundation Fighting Blindness (FFB). Medical writing support, under the direction of the authors, was provided by ApotheCom and funded by ProQR Therapeutics, in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015;163:461–464).