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

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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*

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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.
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%)

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

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

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
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:

<table>
<thead>
<tr>
<th>Name</th>
<th>Stage</th>
<th>Population</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirius</td>
<td>Phase 3</td>
<td>Advanced</td>
<td>BCVA</td>
</tr>
<tr>
<td>Celeste</td>
<td>Phase 3</td>
<td>Early–moderate</td>
<td>Static perimetry</td>
</tr>
</tbody>
</table>

EURETINA September 9–12, 2021 – DG Birch. Phase 1b/2 interim results of QR-421a Stellar trial
Thank you to all Stellar participants and investigators

If you would like further information, please contact:

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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).