Positive results of QR-421a Phase 1/2 Clinical Trial for Usher Syndrome and non-syndromic Retinitis Pigmentosa

March 2021

ProQR has published positive results from its Phase 1/2 Stellar trial of QR-421a, an investigational RNA therapy for the treatment of Usher syndrome and retinitis pigmentosa (RP) due to mutation(s) in exon 13 of the USH2A gene.

About the *Stellar* study

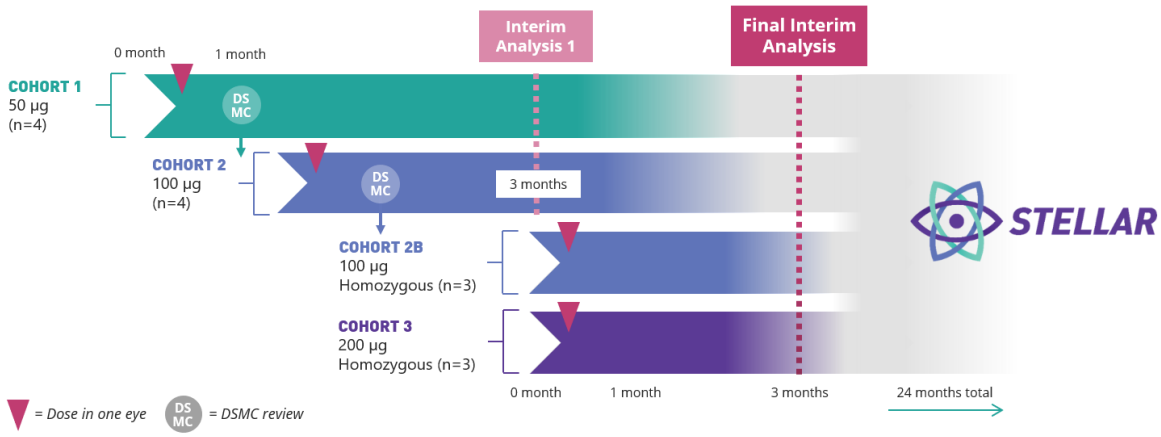
The *Stellar* study is a first-in-human clinical trial of the medicine QR-421a. The Phase 1/2 study includes adults that experience different levels of vision loss due to mutation(s) in exon 13 of the *USH2A* gene. This trial aims to study the safetly profile and efficacy of QR-421a.

QR-421a is an investigational RNA therapy designed to skip exon 13 in the RNA with the aim to stop vision loss.

A total of 20 clinical trial participants took part in the *Stellar* study. The trial design consisted of four study groups of which three groups received QR-421a at three different dose levels. A fourth group received sham treatment, where an intravitreal injection is mimicked but no injection or study drug is given. For each participant one eye was treated with a single injection of QR-421a or sham, and the fellow untreated eye was a control. The graphic below outlines the trial design.

Figure 1. QR-421a Phase 1/2 trial in Usher & nsRP

Enrollment completed; 2nd and final Interim Analysis conducted



Summary of the study results

The *Stellar* study has met all its interim analysis objectives, which included finding a registration endpoint, the dose, dosing interval, and patient population for the future Phase 2/3 pivotal trials.

- QR-421a was observed to be well tolerated with no serious adverse events reported.
- QR-421a also demonstrated benefit in multiple measures of vision, including best corrected visual activity (BCVA), static perimetry, and retinal imaging (OCT).

Furthermore, we have collected the key information to take the program forward, including the appropriate registration endpoint, dose, and dosing interval to be used, and the optimal study population has been identified for the next phase.

ProQR will therefore wind down the *Stellar* study and offer the trial participants a chance to roll over into an open label extension study, named *Helia trial*, where they will be offered continued treatment with QR-421a.

Speaking about the results, Robert Koenekoop, MD, MSc, PhD, FRCS(C), FARVO, a clinical scientist from the Montreal Children's Hospital and Professor of the McGill University Faculty of Medicine and Department of Pediatric Surgery, outlined:

"The safety profile and efficacy findings for QR-421a are very encouraging.

Usher syndrome and non-syndromic retinitis pigmentosa due to USH2A exon 13 mutations are devastating retinal diseases representing a high unmet medical need, as there are no approved therapies to treat the severe vision loss associated with these diseases.

Patients' biggest hope for a therapy is to stop disease progression and prevent vision loss, and these findings suggest that QR-421a has the potential to stabilize vision. I look forward to this exciting program advancing into pivotal trial development."

Safety data

QR-421a was observed to be well tolerated at all doses. There were no serious adverse events noted and no inflammation was observed.

One participant had worsening of pre-existing cataracts in both the treated and untreated eye; both were deemed not treatment related by the clinical trial investigator. One participant had progression of pre-existing cystoid macular edema (CME) that was managed with standard of care. Both cataracts and CME are associated with the natural history of the condition.

Efficacy data

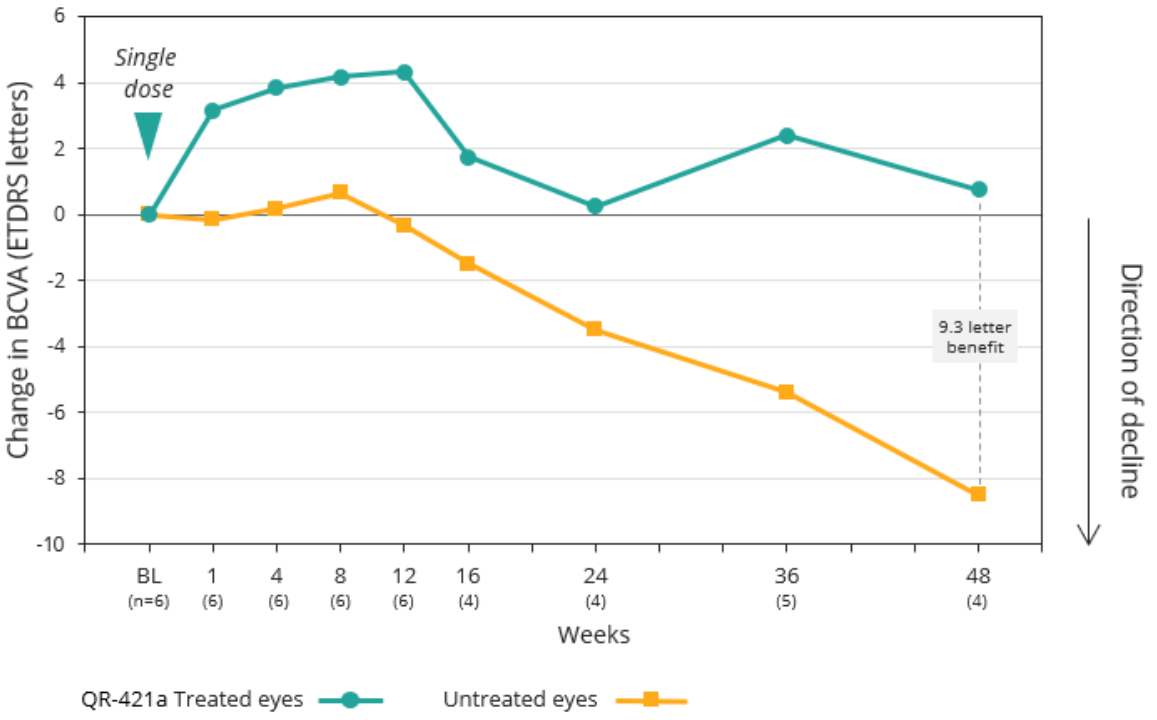
To investigate whether trial participants benefitted from treatment with QR-421a, various vision assessments were done during the study. The outcome of the assessments from the treated eyes were compared with the untreated eyes.

Depending on how advanced the vision loss of a participant was at the start of the study different measures of vision were informative. For individuals with advanced disease, best corrected visual acuity (BCVA), a measure of central vision studied with an eye chart, is very informative. For individuals with early to moderate disease assessing BCVA is less informative because people's central vision has not yet declined. Assessing retinal sensitivity with static perimertry is a more informative measure in this early to moderate group.

After a single injection of QR-421a, participants with advanced disease, showed a stabilization of visual acuity in the treated eye as compared to a natural decline in visual acuity in the untreated eyes. In fact, all advanced participants showed a visual acuity response (of an improvement of 5+ letters from baseline) whereas none of the participants in the sham treated group responded.

Figure 2. Mean change from baseline in BCVA

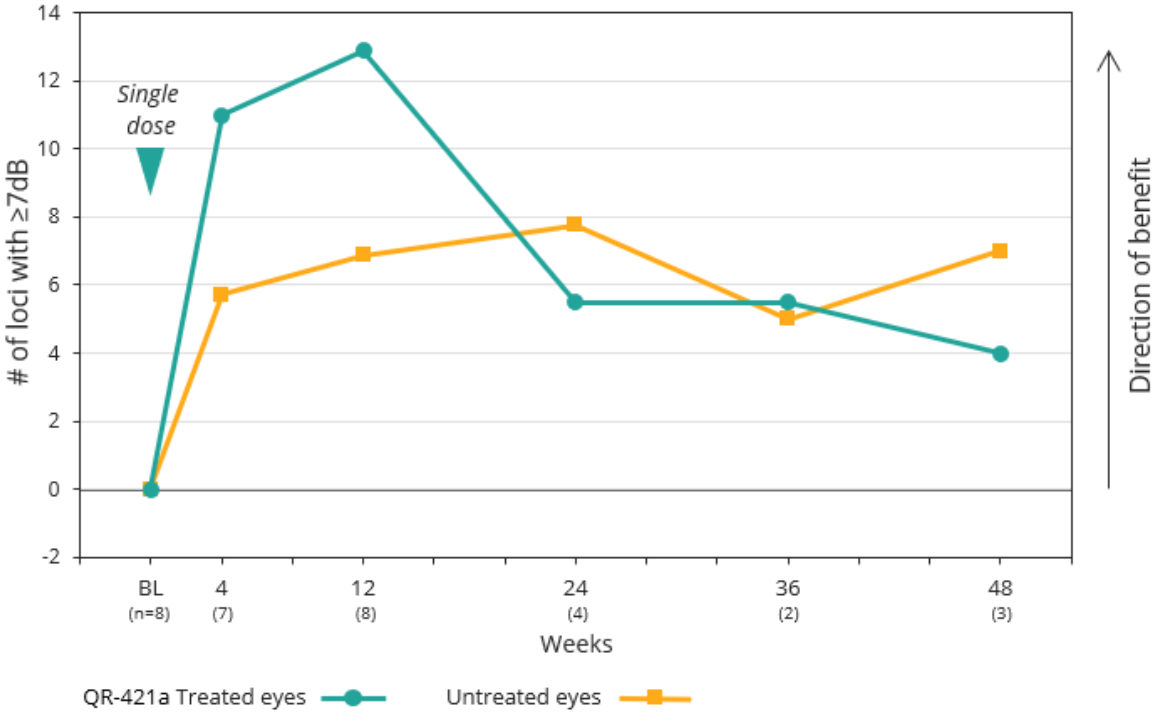
Advanced population (n-6)



In early-moderate participants, retinal sensitivity improved more in the treated eye in comparison to the untreated control eye.

Figure 3. Mean number of retinal loci with ≥7dB improvement in static perimetry

Early-moderate population (n=8)



These positive findings were supported by improvements in other measures including retinal structure as measured by optical coherence tomography (OCT) and retinal sensitivity as measured by microperimetry.

All three doses studied in the Stellar trial were observed to be equally active as predicted by the pre-clinical data. No differences were observed based on participants having one or two mutations in *USH2A* exon 13 or having Usher syndrome or RP. These findings are consistent with the preclinical data for QR-421a.

Next steps

Based on the safety profile and early evidence of efficacy observed to date, ProQR plans to conduct two final stage/pivotal Phase 2/3 clinical trials.

Based on initial regulatory guidance, ProQR plans to submit protocols to start two Phase 2/3 trials. Each trial could potentially serve as the sole registration trial depending on the findings.

A word from Aniz Girach, MD, Chief Medical Officer of ProQR:

"We're pleased to have met all the objectives we set for the Stellar trial, including determining suitable registration endpoints, the dose, dosing interval, and patient population for the Phase 2/3 pivotal trials.

With just a single dose, QR-421a demonstrated clinical proof of concept with benefit observed in treated eyes compared to the untreated eyes in multiple concordant measures of vision. As expected, we see benefits in both advanced and early moderate patients in this slow progressing, debilitating eye disease, allowing us to advance this important therapy for all patients with Usher syndrome and nsRP due to USH2A exon 13 mutations. We have agreed with the Regulators to submit protocols to advance this drug into pivotal testing.

This is our second program targeting a severe inherited retinal disease that is moving into pivotal trials, which further validates our RNA therapy platform and our capabilities to design and efficiently take these programs through clinical development."

The two-final stage/pivotal Phase 2/3 clinical trials, named: *Sirius* and *Celeste*, will study two different patient populations.

The *Sirius* study is a Phase 2/3 trial that will focus on advanced clinical trial participants with BCVA of equal or worse than 20/40. The preliminary design for *Sirius* is a double-masked, randomized, controlled, 24-month, multiple-dose study.

In parallel to *Sirius*, the *Celeste* study is a Phase 2/3 trial focusing on early-moderate clinical trial participants with BCVA of better than 20/40. The preliminary design for *Celeste* is a double-masked, randomized, controlled, 24-month, multiple-dose study.

We value our patient advocacy partners, commenting on the results, Benjamin R. Yerxa, PhD, Chief Executive Officer at the Foundation Fighting Blindness, said:

"There are currently no available treatments for the more than 16,000 patients with Usher syndrome 2A and nsRP due to exon 13 mutations and we are excited about the potential for QR-421a to address this significant unmet need,

We are pleased to see QR-421a advancing to pivotal testing and proud to support the work of ProQR as they advance their pipeline of RNA therapies to potentially help children, adults, and families who are affected by blindness caused by USH2A mutations and other rare inherited retinal diseases."

ProQR thanks the community

The ProQR team would like to thank the study participants, their supporters, the investigators and their staff for the support in the development of QR-421a in this trial.

ProQR remains committed to making a significant and positive impact on the lives of those affected by *USH2A* mediated Usher syndrome and RP. We look forward to continued collaboration and support from the whole Usher and RP community.

Stay in touch

For quarterly news and future study participation opportunities and sign up to the **ProQR Eye Connect Newsletter** or follow us on social media. If you have any questions, please consult your treating physician or you can contact ProQR at **patientinfo@proqr.com**.