Interim Findings of QR-421a Phase 1/2 Clinical Trial for Usher Syndrome and nsRP

March 2020

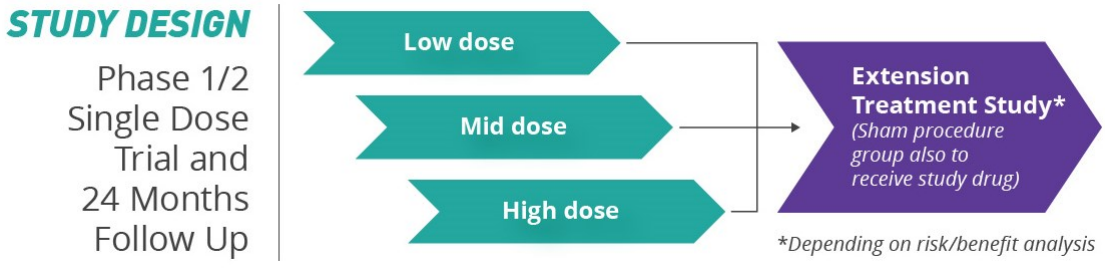
ProQR has published findings from a planned three-month interim analysis of its Phase 1/2 *Stellar* trial of QR-421a, an investigational RNA therapy for the treatment of Usher syndrome and non-syndromic retinitis pigmentosa (nsRP) due to mutation(s) in exon 13 of the *USH2A* gene.

About the *Stellar* study

The first-in-human clinical trial of QR-421a, named *Stellar*, was started in March 2019 and is currently ongoing. The Phase 1/2 study includes adults that experience vision loss due to mutation(s) in exon 13 of the *USH2A* gene. This study is designed to evaluate the safety and tolerability of QR-421a, patient benefit was assessed as well. Participants will be in the study for two years.

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

So far 14 participants were included in the *Stellar* study. Two groups of 4 participants received a single injection into one eye of QR-421a at the low dose (50µg of QR-421a) or the mid dose (100µg of QR-421a), respectively. Another group of 6 participants served as a control in the study, they received a sham procedure where an intravitreal injection was mimicked but no study drug was administered.



Summary of interim findings

After all participants in the first groups had been in the study for at least three months we did an interim analysis. Findings from this analysis suggested QR-421a given as a single intravitreal injection was safe and well tolerated. QR-421a also showed early and encouraging evidence of activity. Two of eight participants in the two treated groups

showed benefit in multiple outcome measures in the treated eye. A similar response was not observed in the six participants included in the control ("sham procedure") group.

Based on these early positive findings we will continue the trial as designed. We will expand the mid dose group by including additional participants. We will also initiate the high dose group. The study is done at expert centers in North America and select European countries.

Interim findings of the Phase 1/2 QR-421a for Usher Syndrome and nsRP

The interim analysis (IA) is based on nine and three month data from the first and second dose groups, respectively, of the *Stellar* Phase 1/2 clinical trial of QR-421a. The *Stellar* trial is a randomized, single ascending dose, global multicenter, longitudinal, 24-month study, involving active treatment with QR-421a versus sham procedure.

The first two groups include a total of 14 participants (ranging from 24-65 years in age), of which eight received a single dose of QR-421a and six received a single sham procedure. Six participants were enrolled in the low dose group, of which four received treatment and two were randomized to sham; eight participants were enrolled in mid dose group of which four received treatment and four were randomized to sham.

The study participants varied in disease characteristics with both Usher syndrome (6 participants) and nsRP (8 participants) affected individuals included, genetic background with both homozygous (4 participants) and heterozygous (10 participants) individuals for *USH2A* exon 13 mutations, and visual impairment at baseline ranging from mild to severe.

Safety data

Across both groups thus far, QR-421a was observed to be generally well tolerated with no serious adverse events noted.

Efficacy data

In the six sham treated participants (two followed for 9 months and four for 3 months), outcome measures demonstrated no consistent pattern of response. In contrast, two of eight QR-421a-treated participants (one each in the low and mid dose groups) demonstrated benefit across multiple concordant outcome measures.

Figure 1. Responder 1: Benefit observed in visual function and retinal structure after a single 50µg dose of QR-421a

30-year-old female with Usher syndrome and moderate visual impairment

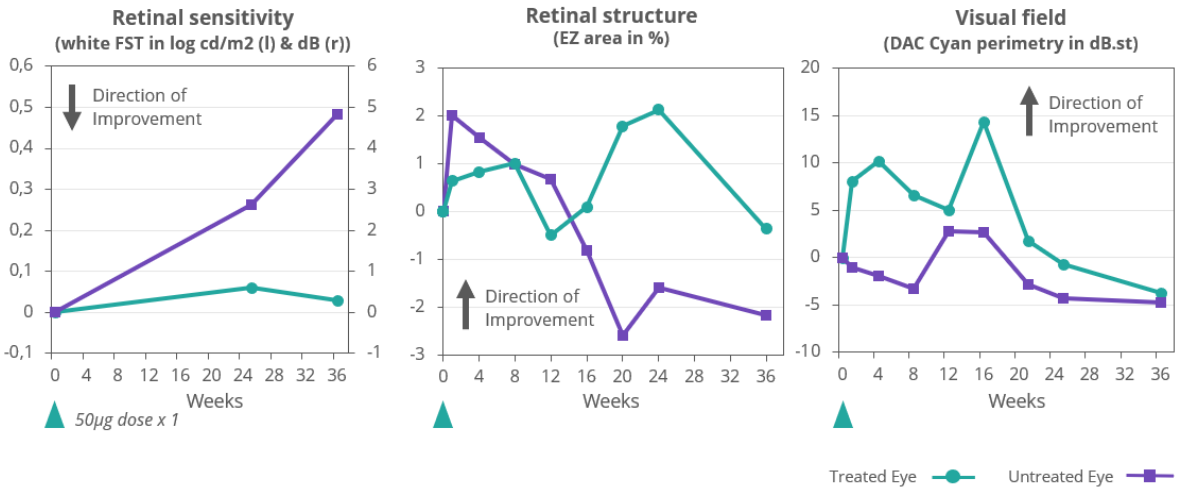


Figure 1. For responder 1 onset of action observed by the 3 month visit. Benefit was maintained for 6 months or longer, which is consistent with the expected half-life of QR-421a in photoreceptors. Benefit was observed across multiple relevant outcome measures appropriate to the severity of the participants' disease, including retinal sensitivity (left graph) measured by full field stimulus threshold test (FST) [deterioration by 5 dB in untreated eye, treated eye remained stable], visual field (middle graph) measured by dark adapted chromatic (DAC) perimetry [15 dB.steradian improvement in peripheral sensitivity in treated eye, less than 5 dB.steradian change in untreated eye], and retinal structure (right graph) measured by optical coherence tomography (OCT) assessment of photoreceptor Ellipsoid Zone (EZ area). For FST and OCT, the untreated eye showed modest deterioration while the treated eye remained stable. For DAC perimetry the untreated eye was unchanged, whereas the treated eye showed improvement.

Figure 2. Responder 2: Benefit observed in visual function after a single 100µg dose of QR-421a

60-year-old male with non-syndromic retinitis pigmentosa and severe visual impairment

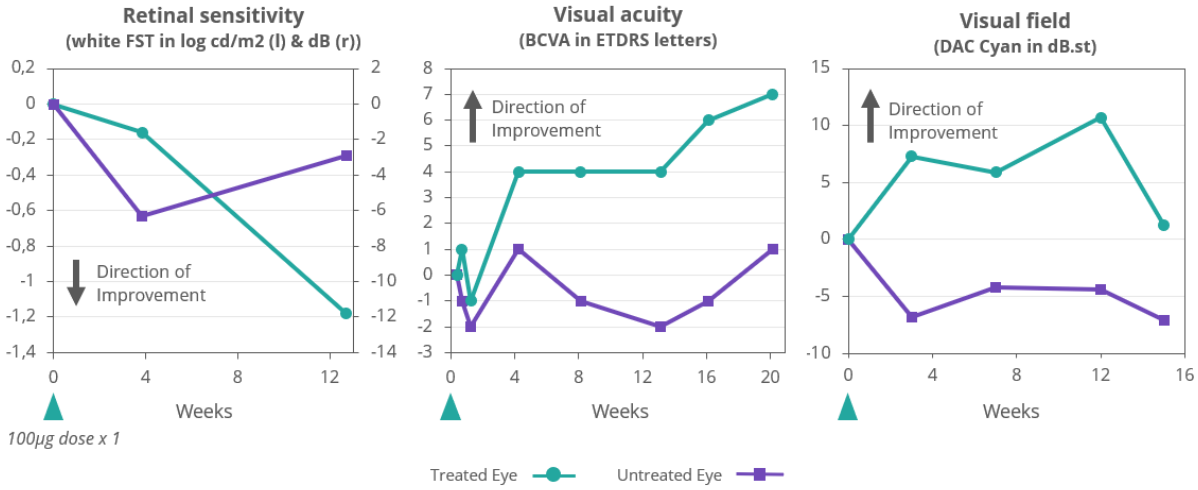


Figure 2. For responder 2 onset of action observed by 3 months. Benefit was observed across multiple relevant outcome measures appropriate for the severity of the participants' disease including retinal sensitivity (left graph) (FST improvement by 12 dB in treated eye, no improvement in untreated eye), visual acuity (middle graph) measured by BCVA (7 letter improvement in the treated eye, which is more than one line on the ETDRS eye chart, compared to no change in the untreated eye) and visual field (right graph) (up to 10 dB.steradian improvement for DAC perimetry in treated eye, with deterioration in the untreated eye).

Next steps

Based on the safety profile and early evidence of efficacy observed to date, ProQR plans to expand the mid dose group with additional individuals who are homozygous for exon 13 mutations (have exon 13 mutations on both copies of the *USH2A* gene) . In parallel a high dose group (200µg of QR-421a) is planned to start. Another interim analysis of safety and efficacy will be planned once all additional participants have reached at least three months of treatment.

A word from David Rodman, M.D., Executive Vice President of Research and Development of ProQR: "The goal of the interim analysis of this 24-month Stellar trial of QR-421a was to assess safety and early signs of efficacy. We did this for the purpose of informing next steps in development and future clinical trial strategy. We are pleased with the current safety profile and are very encouraged by early signals of activity thus far in the trial. The findings support continuing the trial as planned in order to identify a potential development path to registration."

Clinical team thank you

The ProQR team would like to thank the study participants, their caregivers, and 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 Usher Syndrome type 2a and non-syndromic 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.