CLINICAL STUDY PROTOCOL

AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF QR-421a IN SUBJECTS WITH RETINITIS PIGMENTOSA (RP) DUE TO MUTATIONS IN EXON 13 OF THE *USH2A* GENE

Protocol No.	PQ-421a-002
Protocol/Amendment Date:	24 May 2022
Protocol/Amendment No.:	3.0
Protocol Version:	4.0
Supersedes:	3.0
EudraCT/IND Number	2021-002070-93 IND 137660
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands

INVESTIGATOR SIGNATURE PAGE

PRINCIPAL INVESTIGATOR COMMITMENT:

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study drug and the study protocol.

I agree to conduct this clinical study according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all applicable local regulations, Good Clinical Practices (GCP), as well as with the requirements of the appropriate Institutional Review Board(s) (IRB)/Ethics Committee(s) (EC) and any other Institutional requirements.

Printed Name of Principal Investigator

Signature of Principal Investigator

Date (DD Month Year)

PROTOCOL APPROVAL PAGE

An Open-Label Extension Study to Evaluate the Safety and Tolerability of QR-421a in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the *USH2A* Gene

Protocol No.	PQ-421a-002
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Date

ProQR Therapeutics

1.0 SYNOPSIS

<table>
<tr><td>Name of the Sponsor:
ProQR Therapeutics</td><td colspan="2" rowspan="3">Individual Study Table Referring to Part of the Dossier:
Volume: NA
Page: NA</td><td rowspan="3">For National Authority Use Only</td></tr>
<tr><td>Name of Study Drug:
QR-421a Solution for Intravitreal Injection</td></tr>
<tr><td>Name of Active Ingredient:
QR-421a</td></tr>
<tr><td>Title of Study:</td><td colspan="3">An Open-Label Extension Study to Evaluate the Safety and Tolerability of QR-421a in Subjects with Retinitis Pigmentosa (RP) due to Mutations in Exon 13 of the USH2A Gene</td></tr>
<tr><td>Phase of Development:</td><td colspan="3">Phase 2</td></tr>
<tr><td>Study Period:</td><td colspan="3">Anticipated to be 24 months, or until provision of continued treatment by other means is available.</td></tr>
<tr><td>Duration of Subject Participation:</td><td colspan="3">Until provision of continued treatment by other means is available, provided the subject’s benefit-risk assessment remains positive.
Subject participation is expected to be 12 months for subjects who will only receive follow up in this study (i.e., chosen not to have any treatment administered).</td></tr>
<tr><td>Rationale:</td><td colspan="3">There are currently no approved therapies for the treatment of RP due to mutations in exon 13 of the USH2A gene, and disease management is supportive; therefore, a significant unmet medical need exists in this sight-threatening condition.
QR-421a is designed to target mutations in exon 13 of USH2A gene specifically. Hybridization of QR-421a to the pre-messenger ribonucleic acid (pre-mRNA) molecule modulates the ribonucleic acid (RNA) splicing process, which leads to exclusion of exon 13 from the mRNA. The exclusion of exon 13 results in the production of a functional (shorter) usherin protein. It is hypothesized that the production of usherin protein restores the outer segments of the photoreceptors and prevents their degeneration.
Subjects that have participated in QR-421a clinical studies, including study PQ-421a-001, will be given the opportunity to enroll into this extension study for continued dosing and/or follow up.
Study PQ-421a-002 will provide long-term safety, tolerability, and efficacy data of QR-421a.</td></tr>
<tr><td colspan="2">Objectives:
<u>Primary</u>
• To evaluate long-term safety and tolerability of QR-421a
<u>Secondary</u>
• To evaluate long-term efficacy of QR-421a</td><td colspan="2">Endpoints:
<u>Primary endpoints</u>
• Incidence and severity of ocular adverse events (AEs)
• Incidence and severity of non-ocular AEs
<u>Secondary endpoints</u>
• Change from baseline in the following outcome measures:</td></tr>
</table>

• To evaluate long-term systemic exposure of QR-421a	○ Best Corrected Visual Acuity (BCVA) ○ Low Luminance Visual Acuity (LLVA) ○ Ellipsoid Zone (EZ) area/width by spectral domain optical coherence tomography (SD-OCT) ○ Static perimetry ○ Microperimetry • Exposure of QR-421a in serum
Exploratory	**Exploratory efficacy endpoints**

Number of Subjects (planned):	The number of subjects is dependent on the number of eligible subjects that have participated in preceding clinical studies with QR-421a, including 20 subjects from study PQ-421a-001.
Study Design	PQ-421a-002 is an open-label extension study to evaluate the safety, tolerability, and efficacy of QR-421a in subjects with RP due to mutations in exon 13 of the *USH2A* gene. Subjects who have participated in QR-421a clinical studies, including study PQ-421a-001, will be allowed to enrol in this extension study for (continued) dosing, provided the subject's benefit-risk assessment is positive, or for additional follow up. In consultation and agreement with the Medical Monitor, the Investigator will decide on the subject's enrollment upon assessment of the subject's benefit-risk. In consultation and agreement with the Medical Monitor, the Investigator will decide on dosing both eyes. Continued subject treatment in this study will be pursued provided that the benefit-risk balance is positive for the individual subject, as discussed and agreed upon with the Medical Monitor. The same safety monitoring protocol and efficacy assessments will apply to both eyes. Baseline functional and structural measurements for the study and fellow eye will be those from the Screening/Day 1 visit of PQ-421a-002 study. Baseline functional and structural measurements from a previous QR-421a study or historical clinical data may also be used as part of the long-term safety and efficacy analysis.
Study Plan	Subjects in the preceding QR-421a study who have completed the End of Study (EOS) visit as part of study completion/early termination procedures may have the Screening/Day 1 visit for study PQ-421a-002 combined with the EOS visit. All Screening/Day 1 assessments should take place during the EOS visit of the preceding study. If this is not possible, a separate Day 1 should be performed within 12 weeks of the EOS visit. If more than 12 weeks elapse from the EOS visit in the preceding study, a new Screening and Day 1 visit must be performed. Screening and Day 1 may be conducted as a single visit or as two separate visits, (within 12 weeks) as per the Investigator's discretion.

	Subjects in a preceding QR-421a study who did not complete an EOS visit must have a Screening and Day 1 visit performed as part of PQ-421a-002. Screening and Day 1 may be conducted as a single visit or two separate visits (within 12 weeks), as per the Investigator's discretion. Assessments can be completed over multiple, non-consecutive days. Subjects who do not meet stopping criteria prior to their next scheduled injection will receive their planned dose. Subjects who meet stopping criteria will be discontinued from dosing and will be followed for safety and efficacy. The Sponsor, in consultation with the Investigator, may decide to modify the dose, the dosing interval for repeat injections in one eye or both eyes, hold the dose (delay or skip), or discontinue the study drug for an individual subject based on emerging safety and efficacy data and if it is anticipated to be in the best interest of the subject. Stopping criteria are described in Section 4.2.2. Subjects who discontinue study drug in both eyes or who will only receive follow up in this study will be encouraged to remain in the study for observation for at least 12 months post last dose (or post-study initiation for subjects who will only receive follow up). During these 12 months post last dose (or post-study initiation), visits will be planned at 6-month intervals. For subjects who discontinue treatment in one eye, the visits will be reduced to once every 6-month, rather than once every 3 months. After each administration of study treatment, subjects will be monitored clinically for safety, including intraocular pressure (IOP), optic nerve swelling, and signs of inflammation. Efficacy and safety assessments will be performed at selected study visits as indicated in the Schedule of Events (SOE) All ophthalmic assessments will be performed on both eyes. Any assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator or the reading center. Samples for systemic exposure analysis will be collected as indicated in the SOE
Diagnosis and Main Criteria for Eligibility:	**Inclusion Criteria:** 1. Subjects who have participated in a preceding QR-421a study and who may derive benefit from (continued) treatment with QR-421a, and/or continued follow up, as assessed by the Investigator, in consultation and agreement with the Medical Monitor (Section 4.2.1.1). 2. An adult (≥ 18 years) willing and able to provide informed consent for participation prior to performing any study related procedures, and suitable verbal, auditory, written and/or tactile sign language communication as to allow informed consent to be obtained, in the opinion of the Investigator. OR A minor (12 to < 18 years) able to provide age-appropriate assent for study participation, and with a parent or legal guardian willing and able to provide written permission for the subject's participation prior to performing any study related procedures. 3. An adult willing to comply with the protocol, follow study instructions, attend study visits as required and willing and able to complete all study assessments. OR A minor able to complete all study assessments and comply with the protocol and has a parent or caregiver willing and able to follow study instructions and attend study visits with the subject, as required.

	4. Reliable BCVA, perimetry, and other measurements in both eyes, as described in the Study Reference Manual and Imaging Manual and determined by the Investigator. 5. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator.
	Exclusion Criteria: 1. Presence of any significant ocular or non-ocular disease/disorder (or medication and/or laboratory test abnormalities) which, in the opinion of the Investigator and with concurrence of the Medical Monitor, may either put the subject at risk because of participation in the study, may influence the results of the study, or the subject's ability to participate in the study. This includes but is not limited to a subject who has uncontrolled cystoid macular edema (CME) in the treatment eye. CME is permissible if stable for 3 months (with or without treatment). Past CME is permissible if resolved for more than 1 month. 2. Receipt within 3 months prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an IVT injection or planned intraocular surgery or procedure during the course of the study. 3. Safety issue during preceding QR-421a study that may compromise subject safety when continued dosing, as determined by the Investigator and in consultation with the Medical Monitor. a. Subjects with existing safety events from the preceding QR-421a study may be included as determined by the Investigator and in consultation with the Medical Monitor. 4. Current treatment or treatment within the past 12 months with therapies known to influence the immune system (including but not limited to steroid implants, cytostatics, interferons, tumor necrosis factor (TNF)-binding proteins, drugs acting on immunophilins, or antibodies with known impact on the immune system). Subjects that have been treated with systemic steroids within the past 12 months or that require intermittent use of topical steroids may be considered for inclusion following approval by the Medical Monitor. 5. Use of any investigational drug (other than QR-421a) or device within 90 days or 5 half-lives preceding the first dose of study medication, whichever is longer, or plans to participate in another study of an investigational drug or device during the PQ-421a-002 study period. 6. Any prior treatment with genetic or stem-cell therapy for ocular or non-ocular disease. 7. Known hypersensitivity to antisense oligonucleotides or any constituents of the injection. Pregnant and breastfeeding subjects. Females of childbearing potential and males must comply with using highly effective methods of contraception as defined in Section 6.2.2. Women of non-childbearing potential may be included without adequate birth control, provided they meet the criteria in the protocol (Section 6.2.2).
Study Drug, Dosage and Mode of Administration:	QR-421a Solution for IVT injection and solvent; 180 µg loading dose followed by 60 µg maintenance doses at 6-month intervals; IVT injection *Fellow eye is defined as follows*: For subjects previously treated (active or sham) in the preceding QR-421a study: the eye that was not selected as the study eye.

	For subjects that were not treated at all: the eye with the worst BCVA at Helia Screening/Day1. *Study eye is defined as follows:* For subjects previously dosed (active or sham) in the preceding QR-421a study: the eye that was selected as the study eye. For subjects that were not dosed at all: the eye with the best BCVA at Helia Screening/Day1. The Sponsor, in consultation with the Investigator, may decide to modify the dose, the dosing interval for repeat injections in one eye or both eyes, hold the dose (delay or skip), or discontinue the study drug for an individual subject based on the emerging safety and efficacy data and if it is anticipated to be in the best interest of the subject. Stopping criteria are described in Section 4.2.2.
Duration of Treatment:	Anticipated to be 24 months, or until provision of continued treatment by other means is available, provided the subject's benefit-risk determination remains positive.
Reference Therapy, Dosage and Mode of Administration:	Not applicable
Statistical Methods:	Analyses will generally be descriptive. A comprehensive Statistical Analysis Plan (SAP) will specify the statistical methodology, including interim data reviews (if conducted) and table, listing, and figure (TLF) formats for all aspects of the planned analyses.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AON	Antisense Oligonucleotide
AREDS	Age-Related Eye Diseases Study
AST	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CME	Cystoid Macular Edema
CRP	C-Reactive Protein
CSR	Clinical Study Report
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	Ellipsoid Zone
DP	Drug Product
FDA	Food and Drug Administration
FIH	First In Human
GCP	Good Clinical Practice
γGT	Gamma-Glutamyl Transferase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
INR	International Normalized Ratio
IOP	Intraocular Pressure

Abbreviation	Definition
IRB	Institutional Review Board
iPSCs	Induced pluripotent stem cells
IVT	Intravitreal
LCA	Leber's Congenital Amaurosis
LDH	Lactic Dehydrogenase
LLVA	Low Luminance Visual Acuity
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
NSRP	Non-syndromic Retinitis Pigmentosa
PBS	Phosphate buffered saline
PD	Pharmacodynamic
ProQR	ProQR Therapeutics
PT	Preferred Term
RNA	Ribonucleic Acid
RP	Retinitis Pigmentosa
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System Organ Class
SOE	Schedule of Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TLF	Table Listing Figure format
TNF	Tumor Necrosis Factor
US	United States
VF	Visual Field
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

2.0 INTRODUCTION

ProQR Therapeutics (ProQR) is developing an oligonucleotide product, QR-421a, for the treatment of patients with retinitis pigmentosa (RP) caused by mutations in exon 13 of the *USH2A* gene. The primary goal of the development plan for QR-421a is to provide treatment to overcome the genetic defect in patients with pathogenic mutations in exon 13 of the *USH2A* gene, resulting in functional vision restoration or preservation. The intended route of administration is intravitreal (IVT) injection.

2.1 Retinitis Pigmentosa

Retinitis pigmentosa is a clinically and genetically heterogeneous condition and mutations in over 100 genes have been implicated. *USH2A* mutations represent the most common cause of autosomal recessive RP (Hartong 2006).

Pathogenic mutations in the *USH2A* gene disrupt the production of usherin, a protein expressed in photoreceptors where it is required for their maintenance (Liu 2007). In the eye, defects in usherin cause RP. Usherin is also expressed in the ear, where it is required for normal development of cochlear hair cells and hence, normal hearing.

Mutations in exon 13 of the *USH2A* gene result in both non-syndromic and syndromic forms of RP. In the non-syndromic form of RP (NSRP), RP is not associated with other signs and symptoms as part of a genetic syndrome. In the syndromic form, known as Usher syndrome type 2, patients present with congenital moderate to severe hearing loss, and later detection of the retinal disease (ie, RP). Affected patients first experience defective dark adaption, with decreased night vision, around the second decade of life, and subsequent loss of peripheral visual field (VF) when photoreceptor degeneration progresses, eventually leading to only a residual central island of vision, which ultimately progresses to complete blindness. Early onset deafness is attributable to genetic causes in at least 50% of cases (Marazita 1993).

The number of patients with RP due to mutations in exon 13 of the *USH2A* gene is estimated to be around 16,000 in the Western World (United States, Canada, Europe, and Australia) from gene databases. While the hearing deficit in patients with Usher syndrome can be at least partially restored using hearing aids or cochlear implants, there is no approved treatment for the retinal disease in NSRP or RP in Usher syndrome type 2 and disease management is supportive. Vitamin A and docosahexaenoic acid supplementations have been proposed as pharmacological treatment options. Both therapies showed a good safety profile but limited clinical benefit.

2.2 QR-421a for the Treatment of RP due to Mutations in Exon 13 of the *USH2A* Gene

The primary goal of the development plan for QR-421a is to provide treatment to overcome the genetic defect in patients with pathogenic mutations in exon 13 of the *USH2A* gene, resulting in functional vision restoration or preservation.

2.2.1 Nonclinical Experience

2.2.2 Clinical Experience

The clinical development program started in the first half of 2019 with the first-in-human (FIH) clinical study (PQ-421a-001), a Phase 1b/2, double-masked, sham-controlled, dose-escalation study to evaluate the safety and tolerability of QR-421a. An interim analysis was performed in March 2021 and the final participant visit was in Q4 2021. The study is undergoing final analyses and reporting.

Available safety and efficacy data from study PQ-421a-001 support the therapeutic potential observed in the nonclinical studies. Reference is made to the IB for further details.

2.3 Benefit Risk Assessment

RP is a group of inherited eye disorders causing photoreceptor degeneration, leading to progressive vision loss. Affected patients first experience defective dark adaption, peripheral visual field loss when photoreceptor degeneration progresses, and eventually have only a residual central island of vision, which ultimately progresses to complete blindness. There are currently no approved therapies for the treatment of RP patients with mutations in exon 13 of the *USH2A* gene, and disease management is supportive. In addition, these patients usually receive genetic counselling on the risks of passing the condition on to their children and regular medical follow up. They also may receive adaptive support when necessary. Therefore, a significant unmet medical need exists in this sight-threatening condition.

The high unmet medical need in this orphan, sight-threatening condition warrants therapeutic intervention in those patients with usually preserved central vision. In addition, subjects with sufficient residual retinal photoreceptors translated in preserved central VF may derive a clinical benefit (see inclusion criteria of clinical study protocol).

The design of this study has been selected to provide a sufficient benefit-risk ratio to justify the participation of patients. Planned doses are expected to result in retinal concentrations in the efficacious range. In addition, multiple measures are incorporated to ensure the safety of participating subjects.

To address the potential risks defined in the toxicology studies, the reported risks from oligonucleotides administered by IVT injection, and the risks associated with the IVT injection procedure, extensive monitoring to protect subject safety is incorporated in this study and will include assessments of subjects' ophthalmic function and anatomy, in particular, monitoring of anterior, intermediate and posterior segment inflammation by slit-lamp biomicroscopy, clinical lens grading using the Age-Related Eye Diseases Study (AREDS) Clinical Lens Grading

System, monitoring for retinal changes by OCT, and VF testing to monitor changes in retinal sensitivity. This extensive clinical monitoring provides a means to allow early detection and/or prevention of potential AEs such as early signs of macular edema appearance or worsening, decrease in BCVA, the elevation of IOP, intraocular inflammation, lens opacities, and retinal structural modifications. In addition, the visit schedule is designed to monitor subjects one day following IVT injection and a second time within 1 week of IVT injection to monitor for signs of endophthalmitis and intraocular inflammation, consistent with guidelines for IVT injections (Avery 2014).

Detailed information about benefits and potential risks of QR-421a, as well as information on nucleotide AONs as a class of therapeutics can be found in the IB.

2.4 Study Rationale

There are currently no approved therapies for the treatment of RP due to mutations in exon 13 of the *USH2A* gene and disease management is supportive; therefore, an important unmet medical need exists in this condition.

Available safety and efficacy data from study PQ-421a-001 support the therapeutic potential observed in the nonclinical studies and warrant the initiation of the additional clinical studies to confirm benefit-risk.

This extension study allows subjects having participated in QR-421a clinical studies, including study PQ-421a-001, to continue to receive treatment, or follow up, and to observe the long-term safety, tolerability, systemic exposure, and efficacy of treatment with QR-421a. Additionally, this extension study allows for the treatment of the previously untreated fellow/contralateral eye for subjects from study PQ-421a-001.

2.5 Dose Selection

The FIH study PQ-421a-001 evaluated 50, 100 and 200 µg single doses. Safety and efficacy data from 20 subjects followed up for 3 to 24 months have been taken into consideration in the dose selection for the current study. The safety profile of these dose levels did not differ. Available efficacy data confirmed the potential therapeutic value of these dose levels. No clear dose-response was observed. Hence, simulations including nonclinical data were performed to select a dose regimen that will provide exposure levels that maintain a wide safety margin, while at the

same time maximizing pharmacodynamic effects. Additional details on the dose selection are provided in the IB.

TE and FE in Helia are defined in Section 4.2.

QR-421a will be first administered to the fellow eye (as defined in the preceding study) and will be repeated every 6-month. Treatment of the study eye (as defined in the preceding study) can commence 9 months after the treatment of the fellow eye has been initiated and will be repeated every 6-month as well. QR-421a will be administered as a loading dose, followed by maintenance doses at 6-month intervals. The use of a loading dose followed by maintenance doses aims at reaching steady state (efficacious) levels in the retina from the first injection, to maximize clinical response and the potential to provide benefit to the subject. For subjects from study PQ-421a-001 who were administered 50 and 100 µg doses, the loading dose will be 180 µg and the maintenance dose will be 60 µg. The same dosing regimen applies to the fellow eye of subjects from study PQ-421a-001 who were administered 200 µg doses. However, the study eye of these subjects will have a dosing regimen without loading dose and will therefore receive 60 µg in the study eye at Month 9, and every 6-month thereafter, to account for remaining exposure to QR-421a from their initial dose as part of study PQ-421a-001.

2.6 Study Population

Subjects who have participated in a preceding QR-421a study and who may derive benefit from (continued) treatment with QR-421a, and/or continued follow up, as assessed by the Investigator, in consultation and agreement with the Medical Monitor (Section 4.2.1.1).

Reference is made to Section 5.3 for specific eligibility requirements.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of QR-421a.

3.2 Secondary Objective

The secondary objectives of the study are:

- To evaluate the long-term efficacy of QR-421a
- To evaluate the systemic exposure of QR-421a

3.3 Exploratory Objectives

4.0 STUDY OVERVIEW

4.1 Criteria for Evaluation

4.1.1 Primary Endpoints

- Incidence and severity of ocular adverse events (AEs)
- Incidence and severity of non-ocular AEs

4.1.2 Secondary Endpoints

- Change from baseline in the following outcome measures:
    - Best Corrected Visual Acuity (BCVA)

- Low Luminance Visual Acuity (LLVA)
- Static perimetry
- Ellipsoid Zone (EZ) area/width by spectral domain optical coherence tomography (SD-OCT)
- Microperimetry

- Exposure of QR-421a in serum

4.1.3 Exploratory Endpoints

4.2 Study Design

PQ-421a-002 is an open-label, extension study to evaluate the safety, tolerability, and efficacy of QR-421a in subjects with RP due to mutations in exon 13 of the *USH2A* gene.

Subjects that have participated in preceding QR-421a clinical studies, including study PQ-421a-001, will be given the opportunity to enroll into this extension study for continued dosing, provided the subject's benefit-risk assessment is positive, or for additional follow up. The Investigator, in consultation and agreement with the Medical Monitor, will decide on subject's enrollment upon assessment of subject's benefit-risk.

QR-421a will be first administered to the fellow eye and will be repeated every 6-month. Treatment of the study eye can commence as outlined in Section 6.1.5 and based on the participant and when they completed their participation in the previous QR-421a study. The Investigator, in consultation and agreement with the Medical Monitor, will decide on dosing of both eyes. Continued subject treatment in this study will be pursued provided that the benefit-risk is positive for the individual subject, as discussed and agreed upon with the Medical Monitor.

The Sponsor, in consultation with the Investigator, may decide to modify the dose, the dosing interval for repeat injections in one eye or both eyes, hold the dose (delay or skip), or discontinue study drug for an individual subject, based on emerging safety and efficacy data and if it is anticipated to be in the best interest of the subject.

The same safety monitoring protocol and efficacy assessments will apply to both eyes.

Baseline functional and structural measurements for the study and fellow eye will be those from the Screening/Day 1 visit of the current study. Baseline functional and structural measurements from the previous QR-421a study, or historical clinical data, may also be used as part of the long-term safety and efficacy analysis.

Definition of Study Eye and Fellow Eye in Helia

Fellow eye is defined as follows: For subjects previously dosed (active or sham) in the preceding QR-421a study: the eye that was not selected as the study eye. For subjects that were not dosed at all: the eye with the worst BCVA at Helia Screening/Day1.

Study eye is defined as follows: For subjects previously dosed (active or sham) in the preceding QR-421a study: the eye that was selected as the study eye. For subjects that were not dosed at all: the eye with the best BCVA at Helia Screening/Day1.

4.2.1 Study Plan

4.2.1.1 Screening

Subjects in the preceding QR-421a study who have completed the End of Study (EOS) visit as part of study completion/early termination procedures may have the Screening/Day 1 visit for this study combined with the EOS visit. All Screening/Day 1 assessments should take place during the EOS visit of the preceding study. If this is not possible, a separate Day 1 should be performed within 12 weeks of the EOS visit. If more than 12 weeks elapse from the EOS visit in the preceding study, a new Screening and Day 1 visit must be performed. Screening and Day 1 may be conducted as single visit or as two separate visits (within 12 weeks), as per the Investigator's discretion.

Subjects in a preceding QR-421a study who did not complete an EOS visit must have a Screening and Day 1 visit performed as part of PQ-421a-002. Screening and Day 1 may be conducted as a single visit or as two separate visits (within 12 weeks), as per the Investigator's discretion.

During the Screening/Day 1 visit, subjects will be assessed according to the eligibility criteria.

Assessments can be completed over multiple, non-consecutive days instead of 1 full day, at the discretion of the Investigator.

The Investigator, in consultation and agreement with the Medical Monitor, will decide on subject's enrollment upon assessment of subject's benefit-risk and the subject's meeting of eligibility criteria. Continued subject treatment in this study is desirable, but cannot be guaranteed, since it will depend on the risks and benefit of further treatment on a case-by-case basis, as discussed and agreed upon with the Medical Monitor.

4.2.1.2 Study Drug Administration

Subjects will receive study drug via IVT injection in accordance with the procedures outlined by the current international guidelines (AAO 2015; Avery 2014) and as outlined in the Study Reference Manual.

Subjects who do not meet stopping criteria prior to their next scheduled injection will receive their planned dose. Subjects who meet stopping criteria will be discontinued from dosing and will be followed for safety and efficacy. The Sponsor, in consultation with the Investigator, may decide to modify the dose, the dosing interval, hold a specific dose (delay or skip), or discontinue study drug for an individual subject, based on emerging safety and efficacy data and if it is anticipated to be in the best interest of the subject. The Investigator and/or the Sponsor may decide to stop treatment for an individual subject due to an AE. Stopping criteria are described in Section 4.2.2.

Subjects who discontinue study drug in both eyes, or who will only receive follow up in this study, will be encouraged to remain in the study for observation for at least 12 months post last dose (or post study initiation for subjects who will only receive follow up). During these 12 months post last dose (or post study initiation), visits will be planned at 6-month intervals.

For subjects who discontinue treatment in one eye, the visit frequency will be reduced to once every 6-month, rather than once every 3 months.

4.2.1.3 Assessments and Follow-up

On the dosing days post study treatment, subjects will be monitored for safety, including in intraocular pressure (IOP), optic nerve swelling and signs of inflammation. Both post-dose visits (i.e., 1 day after dosing and 7 days after dosing) will be a phone call from the site to the subject, and do not need to be planned if no dosing took place.

All ophthalmic assessments will be performed on both eyes.

The frequency of all assessments is presented in the Schedule of Events (SOE)
See Section 7.2 for details on dosing and follow-up visit procedures. More frequent evaluation may be undertaken for an individual subject to monitor safety at the discretion of the Investigator. Data for all unscheduled visits should be recorded in the electronic case report form (eCRF).

Assessments can be completed over multiple, non-consecutive days instead of 1 full day, at the discretion of the Investigator.

4.2.2 Stopping Criteria

4.2.2.1 Stopping Criteria for Individual Subjects

The Investigator or the Medical Monitor may stop treatment for an individual subject due to an AE (see Section 8.1). The severity of the event(s), as well as the temporal relationship to study drug administration, potential for worsening of the event(s) with continued QR-421a treatment and association with other safety signals or laboratory values should be considered in the decision to stop treatment. The Medical Monitor must be notified of any subject who stops treatment due to an AE. Adverse events considered to be related to the study drug should be taken into account in the benefit-risk assessment.

The Medical Monitor, in consultation with the Investigator, may decide to modify the dose, the dosing interval, hold a specific dose (delay or skip), or discontinue study drug for an individual subject, based on emerging safety and efficacy data and if it is anticipated to be in the best interest of the subject.

Subjects who discontinue study drug in both eyes will be encouraged to remain in the study for observation for at least 12 months post last dose. During these 12 months post last dose, visits can be planned at 6-month intervals.

The Medical Monitor will perform ongoing safety reviews of systemic and ophthalmic safety data and AEs to identify any safety signal.

The Investigator and/or the Sponsor may also decide to stop treatment for both eyes, based on the AE in the first eye.

4.2.2.2 Subject Withdrawal

Subjects are free to withdraw from the study at any time. However, subjects will be encouraged to remain in the study for safety follow-up whenever possible through the EOS visit. A subject who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator should follow up on AEs outside of the clinical study to ensure subject safety; however, no data on such events will be collected for study purposes.

4.2.3 Discontinuation of the Study

The Medical Monitor will evaluate the safety and tolerability data as described in Section 2.2.2 and thereafter on an ongoing basis to recommend if the study should continue or cease, or if any modifications should be made as to how subjects are treated or managed.

5.0 SELECTION OF STUDY POPULATION

5.1 Study Population

Subjects who have participated in a preceding QR-421a study and who may derive benefit from (continued) treatment with QR-421a, and/or continued follow up, as assessed by the Investigator, in consultation and agreement with the Medical Monitor, and meet all eligibility requirements, are eligible to participate in this extension study.

5.2 Selection of Subjects

Subjects will be evaluated against all eligibility criteria as presented in the SOE
Final approval from the Sponsor's medical monitor on subject eligibility is required prior to dosing of subjects.

Results of assessments for all eligibility criteria must be available and reviewed prior to the subject's first dose of study treatment. Subjects who have been identified as screen failure may be rescreened if, in the opinion of the Investigator, there is a reasonable chance that the subject may become eligible at a later time point (for example, when awaiting a 3-month window after intraocular surgery).

5.3 Eligibility Criteria

5.3.1 Inclusion Criteria

The subject is eligible for the study if all the following inclusion criteria apply at baseline:

1. Subjects who have participated in a preceding QR-421a study and who may derive benefit from continued treatment with QR-421a, and/or continued follow up, as assessed by the Investigator, in consultation and agreement with the Medical Monitor (Section 4.2.1.1).
2. An adult (≥ 18 years) willing and able to provide informed consent for participation prior to performing any study related procedures, and suitable verbal, auditory, written and/or tactile sign language communication as to allow informed consent to be obtained, in the opinion of the Investigator.

   OR

   A minor (12 to < 18 years) able to provide age-appropriate assent for study participation, and with a parent or legal guardian willing and able to provide written permission for the subject's participation prior to performing any study related procedures.

3. An adult willing to comply with the protocol, follow study instructions, attend study visits as required and willing and able to complete all study assessments.

   OR

   A minor able to complete all study assessments and comply with the protocol and has a parent or caregiver willing and able to follow study instructions and attend study visits with the subject, as required.
4. Reliable BCVA, perimetry, and other measurements in both eyes, as described in the Study Reference Manual and Imaging Manual and determined by the Investigator.
5. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator.

5.3.2 Exclusion Criteria

The subject is ineligible for the study if any of the following criteria apply at Screening:

1) Presence of any significant ocular or non-ocular disease/disorder (or medication and/or laboratory test abnormalities) which, in the opinion of the Investigator and with concurrence of the Medical Monitor, may either put the subject at risk because of participation in the study, may influence the results of the study, or the subject's ability to participate in the study. This includes but is not limited to a subject who has uncontrolled cystoid macular edema (CME) in the treatment eye. CME is permissible if stable for 3 months (with or without treatment). Past CME is permissible if resolved for more than 1 month.
2) Receipt within 3 months prior to Screening of any intraocular or periocular surgery (including refractive surgery), or an IVT injection or planned intraocular surgery or procedure during the course of the study.
3) Safety issue during preceding QR-421a study that may compromise subject safety when continued dosing, as determined by the Investigator, and in consultation with the Medical Monitor.
   a) Subjects with existing safety events from the preceding QR-421a study may be included as determined by the Investigator and in consultation with the Medical Monitor.
4) Current treatment or treatment within the past 12 months with therapies known to influence the immune system (including but not limited to steroid implants, cytostatics, interferons, tumor necrosis factor (TNF)-binding proteins, drugs acting on immunophilins, or antibodies with known impact on the immune system). Subjects that have been treated with systemic steroids within the past 12 months or that require intermittent use of topical steroids may be considered for inclusion following approval by the Medical Monitor.
5) Use of any investigational drug (other than QR-421a) or device within 90 days or 5 half-lives preceding the first dose of study medication, whichever is longer, or plans to participate in another study of an investigational drug or device during the PQ-421a-002 study period.
6) Any prior treatment with genetic or stem-cell therapy for ocular or non-ocular disease.

7) Known hypersensitivity to antisense oligonucleotides or any constituents of the injection.
8) Pregnant and breastfeeding subjects. Females of childbearing potential and males must comply with using highly effective methods of contraception as defined in Section 6.2.2. Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in the protocol (Section 6.2.2).

6.0 STUDY DRUG AND CONCOMITANT THERAPIES

6.1 Study Drug

6.1.1 Study Drug Description and Supply

The QR-421a study drug is a solution for IVT injection.

Please refer to the Pharmacy Manual and Study Reference Manual for additional details.

6.1.2 Placebo

No placebo is used.

6.1.3 Study Drug Shipment and Storage

Please refer to the Pharmacy Manual and Study Reference Manual for details on shipment, storage, handling, preparation, and administration.

6.1.4 Study Drug Accountability and Reconciliation

The Investigator must designate a research pharmacist or other staff member to maintain an inventory record of drugs received and dispensed. Additional details on study drug handling are provided in the Pharmacy Manual and the Study Reference Manual.

6.1.5 Dosage and Administration

The study eye is the study/treatment eye as defined in the preceding QR-421a study; the fellow eye is the fellow/contralateral eye as defined in the preceding QR-421a study. In general, QR-421a will be administered as a 180 µg loading dose on day 1, followed by 60 µg maintenance doses at 6-month intervals. Modifications for individual participants, defined based on the dosing and/or timing of their participation completion in the previous QR-421a study are outlined below.

QR-421a will be administered via IVT injection in accordance with the procedures outlined by the American Academy of Ophthalmology (Avery 2014). The pharmacist (or other personnel qualified to prepare study drug for administration) at each study center will receive study drug and will prepare and/or dilute the study drug with sterile solvent (PBS) when necessary, according to the Pharmacy Manual for each administration.

Administration of study drug will only be performed by qualified ophthalmologists in an in-clinic setting. No other medications should be mixed with study drug. Reference is made to the Pharmacy Manual and Study Reference Manual for detailed instructions on the IVT injection.

6.2 Concomitant Medications and Auxiliary Therapy

6.2.1 Prohibited Concomitant Medications

The use of any investigational drug (other than QR-421a) or device within 90 days or 5 half-lives of the drug at Day 1, whichever is longer, or plans to participate in another clinical study during the study period is prohibited. Medications that are known to be toxic to the lens, retina, or optic nerve are prohibited. These may include, but are not limited to systemic/intraocular steroids, amiodarone, deferoxamine, chloroquine/hydroxychloroquine sulfate, tamoxifen, phenothiazines, and ethambutol, etc. Topical steroids are not prohibited but should only be used following consultation with the Medical Monitor.

During the study, use of any new medication or change in the dose of a medication that may have side effects on vision will need to be reviewed and approved by the Medical Monitor.

6.2.2 Adequate Forms of Birth Control

Women of childbearing potential (WOCBP; ie fertile, following menarche and until becoming postmenopausal unless permanently sterile) and fertile male subjects (ie, after puberty unless permanently sterile) must either practice true abstinence in accordance with their preferred and usual lifestyle, or agree to use highly effective methods of contraception for up to 24 months following their last dose of QR-421a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A man is considered fertile unless permanently sterile by bilateral orchiectomy or has undergone vasectomy and received medical assessment of surgical success.

Highly effective methods of birth control include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that the partner is the sole sexual partner and has received medical assessment of the surgical success)
- Sexual abstinence: sexual abstinence must be true abstinence which is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception

Double barrier methods (a combination of condom with cap, diaphragm, or sponge with spermicide) are not considered highly effective.

Women of non-childbearing potential (ie, not fertile, before menarche, postmenopausal, or permanently sterilized) may be included without the use of adequate birth control, provided they meet the criteria in the protocol.

Birth control measures must be employed during the time of participation (beginning at the Screening Visit) in this study

A man who is fertile should use a condom during treatment

7.0 STUDY VISITS

All study visits, assessments and procedures should be completed as indicated per the SOE

7.1 Visit and Assessment Windows

For those procedures for which a specific time point post dose is required (eg, systemic exposure blood draws), the protocol refers to nominal times. Actual times for such assessments are to be recorded in the source documentation and in the eCRFs, and if any time points are missed, the

reasons are also to be recorded. For more details, please refer to the case report form completion guidelines.

Subjects in the preceding QR-421a study who have completed the EOS visit as part of study completion/early termination procedures may have the Screening/Day 1 visit for this study combined with the EOS visit. All Screening/Day 1 assessments should take place during the EOS visit of the preceding study. If this is not possible, a separate Day 1 should be performed within 12 weeks of the EOS visit. If more than 12 weeks elapse from the EOS visit in the preceding study, a new Screening and Day 1 visit must be performed. Screening and Day 1 may be conducted as a single visit or as two separate visits (within 12 weeks), as per the Investigator's discretion.

Subjects in a preceding QR-421a study who did not complete an EOS visit must have a Screening and Day 1 visit performed as part of PQ-421a-002. Screening and Day 1 may be conducted as a single visit or as two separate visits (within 12 weeks), as per the Investigator's discretion.

During the Screening/Day 1 visit, subjects will be assessed according to the eligibility criteria.

Dosing day visits have a visit window of ± 30 days. Study center phone calls to the subjects will occur 1 and 7 (±3) days post-IVT injection. All visits and/or assessments can be completed over multiple, non-consecutive days.

All visit windows should be calculated from Day 1 in this study.

7.2 Dosing and Follow-up Visits

Dosing visits occur on Day 1, and then every 6-month for the fellow eye. Dosing visits for the study eye will begin at Month 3 or Month 9 (see Section 6.1.5 on dosing schema by participant and preceding QR-421a study), and then every 6-month. The (eventual) between-eye interval of every 3 months could be adapted in agreement with the Medical Monitor if safety data are supportive, and for logistic reasons.

Subjects should be monitored for safety, including IOP, optic nerve swelling and signs of inflammation during the post-injection period.

Study center phone calls to the subjects will occur 1 day and 7 (±3) days post-IVT injection. These calls are only required if the subject received a dose.

All follow-up study visits, assessments and procedures should be completed as indicated per the SOE Subjects will be assessed for safety, tolerability, and efficacy at follow-up visits with all ophthalmic assessments performed on both eyes.

Subjects who discontinue study drug in both eyes, or who will only receive follow up in this study, will be encouraged to remain in the study for observation for at least 12 months post last

dose (or post study initiation for subjects who will only receive follow up). During these 12 months post last dose (or post study initiation), visits can be planned at 6-month intervals.

For subjects who discontinue treatment in one eye, the visit frequency can be reduced to once every 6-month, rather than once every 3 months.

7.3 End of Study Visit

The EOS visit occurs 12 months after the last dose of study drug for a subject.

Subjects who discontinue study treatment but do not withdraw consent will be encouraged to remain in the study for observation for at least 12 months post last dose.

8.0 STUDY ASSESSMENT PROCEDURES

If a subject is unable to complete a specific assessment, this should be recorded in the eCRF and the subject's ability reassessed at the next specified visit. All attempts at performing assessments should be recorded. Any assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator.

All assessments will be conducted as indicated by the SOE

8.1 Adverse Events

Information regarding occurrence of AEs will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment, and relationship to study drug will be recorded. Refer to Section 9.0, Assessment of Safety or Adverse Events and Serious Adverse Events, for further details.

8.2 Laboratory Evaluations

At Screening, laboratory results from the preceding QR421a study will be reviewed (if within the 12-week window), or a new local or central laboratory test, including a urine dipstick, will be performed to review for any abnormal laboratory values that may indicate a safety signal that would affect eligibility.

Subsequent laboratory evaluations will be conducted at a central laboratory and include serum chemistries, hematology and urinalysis. Reference ranges for all laboratory parameters are provided in the Laboratory Manual. See Appendix 2 for a list of laboratory tests to be conducted.

Serum chemistries will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (γGT), C-reactive protein (CRP), alkaline phosphatase (ALP), total and direct bilirubin, lactic dehydrogenase (LDH), albumin, and total

protein. Estimated glomerular filtration rate (eGFR) is to be calculated using the CKD-EPI Creatinine Equation 2009 calculation.

Hematology will include a complete blood count (CBC): CBC with absolute differential (hematocrit, hemoglobin, white blood cell count [WBCs], red blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count).

Coagulation panel: prothrombin time and International Normalized Ratio (INR).

Urinalysis (by visual inspection and dipstick) will include color and appearance, specific gravity, pH, protein, glucose, blood (erythrocytes), leukocytes, bilirubin, ketones, nitrite, and urobilinogen.

Repeat laboratory tests are permitted to confirm potentially spurious values or false positive results, at the discretion of the Investigator. Repeat analysis results for any laboratory assessments that may affect eligibility should be discussed with the Medical Monitor prior to subject inclusion.

For female subjects of childbearing potential, pregnancy testing will be performed per the SOE

8.3 Systemic exposure

Samples for systemic exposure analysis of QR-421a will be collected from all subjects as indicated per the SOE

8.4 Ophthalmic Examinations

Ophthalmic examinations include slit lamp biomicroscopy, intraocular pressure, and dilated fundus examination and will be performed according to the SOE
Biomicroscopic examination includes pupillary examination, and examination of the external adnexa, conjunctiva, sclera, cornea, anterior chamber flare and cell score, iris, lens grading using the Age-Related Eye Diseases Study (AREDS) lens grading system, and vitreous examination. Intraocular pressure will preferably be assessed using Goldmann applanation tonometry. The same equipment should be used consistently throughout the study for a particular subject. Funduscopic examination (dilated) includes evaluation of optic nerve, macula, retinal vessels, and retinal periphery.

Following administration of study treatment, intraocular pressure and perfusion of the optic nerve head should be monitored and managed appropriately. Subjects should also be monitored for signs of inflammation during the post dosing period.

Further details on the procedures for ophthalmic examinations are in the Study Reference Manual.

8.5 Spectral Domain Optical Coherence Tomography

Spectral domain optical coherence tomography (SD-OCT) will be performed according to the SOE . Changes in SD-OCT findings are of relevance to the safety and efficacy profile of QR-421a. All SD-OCT scans should be performed in accordance with the procedures outlined in the Imaging Manual.

8.6 Efficacy Assessments

Efficacy assessments include static and microperimetry, SD-OCT, BCVA, and LLVA, and will be performed at selected study visits as indicated in the SOE See the Study Reference Manual and Imaging Manual for further information on these assessments. All ophthalmic assessments will be performed on both the study and fellow eye. A central reading center will be used for several of the ophthalmologic assessments, including SD-OCT.

BCVA and LLVA will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) vision chart. LLVA will be measured by reading an ETDRS chart under normal lighting with a 2.0-log-unit neutral density filter placed in front of the best lens correction (Sunness 2008).

8.7 Retinitis Pigmentosa Medical History

The following information related to subjects RP due to mutations in exon 13 of the USH2A gene will be collected:

9.0 ASSESSMENT OF SAFETY OR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All subjects who receive study treatment will be assessed for safety.

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor regarding any event that seems unusual, even if this event may be

considered an unanticipated benefit to the subject. The Investigator is responsible for appropriate medical care of subjects during the study and may add unscheduled visits, additional exams/tests for safety purposes.

9.1 Definitions of Adverse Event, Serious Adverse Event, and Suspected Unexpected Serious Adverse Event

9.1.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related or not. Adverse events can include any unfavorable, noxious, unintended sign, symptom, or disease temporally associated with use of a study drug or other protocol-imposed intervention, regardless of attribution. Adverse events may be spontaneously reported by the subject, discovered by Investigator questioning, or detected through laboratory test, or other means.

Adverse events include:

- Pre-existing medical conditions judged by the Investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period (as specified in Section 9.3.1)
- Adverse events not previously observed in the subject that emerge during the protocol-specified AE reporting period (as specified in Section 9.3.1)
- Complications that occur as a result of protocol-mandated interventions
- Adverse events that occur prior to study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as blood draws, sedation prior to IVT injection)

9.1.2 Serious Adverse Events

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE. This definition implies that the subject, in the view of the Investigator, is at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongs existing hospitalization, except for planned hospitalization
- Persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject’s ability to conduct normal life functions)

- Congenital anomaly or birth defect. This serious criterion applies if a congenital anomaly/birth defect is diagnosed in a child born to a female subject, or a female partner of a male subject exposed to the study drug
- Other important medical events. Medical and scientific judgment should determine whether an AE should be classified as serious in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above.

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs. Surgery for lens opacity removal (lens replacement) is not considered a serious AE as it does not require the subject be admitted to a hospital unit based on the nature of the surgery. Even in the case where the subject may be hospitalized for convenience, or a subject is too frail to make the commute back and forth to the surgical center, it is still not a Serious AE (SAE). The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache) (see Section 9.2.1). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the AE eCRF and SAE form.

9.1.3 Suspected Unexpected Serious Adverse Reaction Definition

In order to be qualified as a suspected unexpected serious adverse reaction (SUSAR), the AE must meet 3 criteria: the event is serious, there is a certain degree of probability that the event is a reaction to the study drug being researched and the nature and severity of the reaction are not in agreement with the product information (i.e., the reaction is unexpected as per the reference safety information). All SUSARs will be reported as required to the Competent Authorities and to the Ethics Committee (EC)/Institutional Review Boards (IRBs) of the countries and centers concerned.

9.1.4 Adverse Events of Special Interest

9.2 Assessment of Adverse Events

The Investigator is responsible for assessing the seriousness, severity and causality of AEs.

9.2.1 Assessment of Severity (Intensity) of Adverse Events

On the AE eCRF, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- MILD: Does not interfere with subject's usual function.
- MODERATE: Interferes to some extent with subject's usual function.
- SEVERE: Interferes significantly with subject's usual function.

As described previously in Section 9.1.2, note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event and may not meet the regulatory definition of serious. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as a serious AE unless it met one of the regulatory criteria for SAEs, listed above in Section 9.1.2.

Any change in severity should be noted in the eCRF, e.g., a change from mild to severe or a change from severe to moderate should be noted with the start and stop dates for each intensity.

9.2.2 Assessment of the Relationship of Adverse Events to Study Drug

The Investigator will make a causality assessment about the relationship of each AE to study drug. To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

Not Related: The AE has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after dose of study drug).

Related: An AE that is related to the study drug or its administration (i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that could not be reasonably explained by the known characteristics of the subject's clinical state).

For all AEs and SAEs, Investigators will make separate assessments of causality about the relationship of the event to study drug and to study procedures (i.e., IVT injection).

Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process and will be recorded in the subject's medical record, AE eCRF, or paper AESI/SAE/Special Situation form if applicable. Adverse events recorded without the Investigator's assessment of the relationship to study drug will be followed up until causality is assigned.

9.2.3 Assessment of the Outcome of Adverse Events

The Investigator will record the outcome of AEs and SAEs using the following criteria:

- **Recovered/resolved:** The subject has fully recovered from the event, with no residual effects observable.
- **Recovered/resolved with sequelae:** The subject has recovered from the event, but with residual sequelae effects observable.
- **Not recovered/resolved:** Effects of the event are still present.
- **Recovering/resolving:** The subject has improved but has not fully recovered from the event.
- **Fatal:** The death is related to the event.
- **Unknown:** The outcome of the event is unknown to the reporter (eg, subject was lost to follow-up).

9.3 Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs are recorded in the subject's medical record, AE eCRF, or paper AESI/SAE/Special Situation form, and reported to the Sponsor in accordance with protocol instructions. The AE eCRF can be used to report both AEs and SAEs. If necessary, e.g., in case of failure of the Electronic Data Capture (EDC) system or for logistical reasons, a paper AESI/SAE/Special Situation form may be used instead.

9.3.1 Adverse Event Reporting Period

After signing of the Informed Consent all significant medical conditions including signs/symptoms of the underlying disease and known pre-existing medical conditions found during the screening period and up to initiation of dosing will be captured as medical history. This includes (ongoing) AEs from the preceding study. Any event/condition, including those related to participation in the study or study procedures, those not related to underlying disease or pre-existing medical conditions already part of medical history, and occurring before first dose of study treatment will be captured as a non-treatment emergent AE.

Any event/condition noted once the subject receives their dose of study drug will be captured as an AE. All AEs and SAEs regardless of attribution will be collected until at least 90 days following the last administration of study drug or the subject's EOS visit, whichever is later. At the last scheduled visit, the Investigator should instruct each subject to report to the Investigator any subsequent AEs/SAEs that the subject's personal physician believes could be related to prior study treatment.

SAEs unrelated to study treatment and non-serious AEs are to be followed until the last scheduled study visit (EOS visit), with the outcome at that point of time to be recorded in the eCRF. SAEs related to study treatment are to be followed until resolution or until they return to baseline, stabilize, or the subject is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF or paper AESI/SAE/Special Situation form (if applicable) and in the subject's medical record to facilitate source data verification. For some SAEs, the Sponsor or its designee may follow up by telephone, facsimile, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (eg, hospital discharge summary, consultant report, or autopsy report).

9.3.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

9.3.3 Recording Adverse and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF or paper AESI/SAE/Special Situation form. Colloquialisms and abbreviations should be avoided. Serious AEs must also be recorded on the AE eCRF or paper AESI/SAE/Special Situation form. Only 1 medical concept should be recorded in the event field on the AE eCRF or paper AESI/SAE/Special Situation form (if applicable).

a. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should also be entered as separate AEs. For example, if severe diarrhea is known to have resulted in dehydration, both diarrhea and dehydration should be entered as AEs on the eCRF, and if also serious, as SAE on AE eCFR or paper AESI/SAE/Special Situation form (if applicable).

b Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe or occurs more frequently, it should be recorded again on the AE eCRF with the increased severity grading.

A recurrent AE is one that occurs and resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the AE eCRF.

c. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs on the eCRF or paper AESI/SAE/Special Situation form (if applicable).

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the eCRF or paper AESI/SAE/special situation form (if applicable), unless their severity, seriousness, or etiology changes.

d. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 9.3.1), regardless of attribution, will be recorded on the AE eCRF or paper AESI/SAE/Special Situation form and reported to the Sponsor within 24 hours of event knowledge.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as a single medical concept. For example, if death resulted from respiratory failure, the AE recorded should be "Respiratory Failure", and the outcome of the AE would be "Death". If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death" on the AE eCRF or paper AESI/SAE/Special Situation form.

e. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE eCRF or paper AESI/SAE/Special Situation form (if applicable), it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

f. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

g. Pregnancy

If a female subject or a female partner of a male subject becomes pregnant during study participation of the female subject or the male partner, a Pregnancy Report form should be completed and faxed to the Sponsor within 24 hours of learning of the pregnancy, using the fax numbers listed in the Study Reference Manual.

Abortion, whether therapeutic or spontaneous, will also be reported on a Pregnancy Report form and faxed to the Sponsor. Refer to the Study Reference Manual for forms and complementary reporting information. If the abortion meets seriousness criteria (see Section 9.1.2, Serious Adverse Event Definition), this information will be captured on the AE eCRF or paper AESI/SAE/Special Situation form (if applicable).

Pregnancy should be followed up until after delivery or termination of the pregnancy. Any congenital anomaly/birth defect in a child born to a female subject or to a female partner of a male subject exposed to the study drug should be recorded and reported as an SAE.

h. Special Situations Reporting

Medication errors and uses outside what is foreseen in the protocol, including overdose and occupational exposure must be reported to the Sponsor within 24 hours from awareness on a paper AESI/SAE/Special Situation Form and an AE eCRF for tracking purposes and will be considered a protocol deviation. Overdose is defined as any study drug dose administered above

the intended dose. Additional instructions for reporting special situation information will be provided by the Sponsor at the time of notification.

9.4 Serious Adverse Events Notification

For all SAEs, regardless of suspected causality, a completed AESI/SAE/Special Situation form must be sent within 24 hours of discovery of the event to:

DRUG SAFETY

See Study Reference Manual

Any fatal or life-threatening (ie, imminent risk of death) event that is attributed by the Investigator to the study drug must be immediately telephoned to:

DRUG SAFETY

Phone: See Study Reference Manual for phone number

followed by submission of written case details on an AESI/SAE/Special Situation form within 24 hours.

Serious AEs occurring any time after study participation that are considered by the Investigator to be possibly related to study drug must also be reported. The following are important points to remember when completing the AESI/SAE/Special Situation form:

- If complete information is not available, at a minimum, subject identifier, suspect drug, study center identifier, event or outcome, and Investigator assessment of causal relationship to study drug should be provided.
- A rationale for the causality assessment of an SAE should always be included, so that a better understanding of the event can be compiled.
- Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event should be submitted by revising the AESI/SAE/Special Situation form as soon as the information becomes available. Copies of source documents, with subject identifiers redacted, should be submitted only when they are written in English. If source documents are not in English, the Investigator must summarize the source documents, providing a complete English narrative that includes a description of the events as it evolved, the results of all diagnostic procedures performed, treatments administered, and outcome of the event. A query regarding a follow-up report should be answered within 5 working days from receipt of the query.
- Appropriate diagnostic tests and therapeutic measures are to be performed as necessary and reported on the AESI/SAE/Special Situation form.

- All SAEs must be reported to the IRB/EC, if applicable. See the International Council for Harmonisation (ICH) GCP E6 (R2), Section 4.11.1 (ICH 2016).

9.5 Expedited Reporting of Suspected Unexpected Serious Adverse Reactions

- The Sponsor or its designee is responsible for notifying the study centers of all expedited SAEs that occur during any clinical studies that are using the study drug. The Sponsor or its designee shall also notify Central ECs and Central IRB of SUSARs or significant risks to subjects, per country requirements. All SUSARs will be reported as required to the Competent Authorities of all involved participating countries.
- The Investigator will notify local IRB/EC of SUSARs or significant risks to subjects, per local country requirements. The Investigator must keep copies of all AE information, including correspondence with the Sponsor or local IRB/EC on file.
- All studies that are conducted within any European country will comply with the European Clinical Trial Directive 2005/28/EC, the Clinical Trial Directive 2001/20/EC, and the Detailed Guidance CT-3 (2011/C 172/01) and Regulation 536/2014.

10.0 STATISTICAL METHODOLOGY

10.1 General Considerations

A comprehensive Statistical Analysis Plan (SAP) will specify the statistical methodology, including interim data reviews (if conducted) and table, listing, and figure (TLF) formats for all aspects of the planned analyses. The SAP supports the completion of the Clinical Study Report (CSR) for this protocol.

All AEs will be considered in determining the safety profile of QR-421a. As an early phase clinical study, exploratory analyses not necessarily identified in the SAP may be performed to support the clinical development program. Any p values that will be calculated according to the analysis plan will be interpreted in view of the exploratory nature of the study. Any post hoc, or unplanned, analyses not identified in the SAP will be clearly identified in the CSR, in accordance with applicable Standard Operating Procedures of the sponsor.

10.2 Determination of Sample Size

The sample size is determined by the number of subjects completing preceding QR-421a studies, including PQ-421a-001, who meet the inclusion and exclusion criteria and provide informed consent.

10.3 Randomization and Masking

This is an open-label study; randomization and masking are not required.

10.4 Replacement of Subjects

Not applicable as this is an extension study.

10.5 Analysis Populations

All Screened Subjects: All subjects who provided informed consent to participate in the study.

Safety Population: the population for safety analysis will consist of all subjects who receive any QR-421a.

Efficacy Evaluable Population: All subjects who received at least one dose of study treatment and had at least 1 baseline observation or measurement. The Efficacy Evaluable Population will be defined separately for each endpoint, based on availability of at least 1 baseline measurement of that endpoint.

Per Protocol Efficacy Population: All subjects in the Efficacy Evaluable Population except for subjects with major protocol deviations. The list of major protocol deviations selected for exclusion from this population will be completed prior to database lock. The Per Protocol Population will also be defined separately for each endpoint.

10.6 Subject Disposition, Demographics and Baseline Disease Characteristics

Subject disposition, baseline demographics and disease characteristics will be summarized for all subjects combined, and potentially grouped by baseline characteristics. Such grouping of subject disposition, demographics and disease characteristics by baseline characteristics will be described in the SAP.

10.7 Treatment Compliance

All doses are observed and administered by study staff. Treatment compliance will be determined by source records documenting treatment observations and summarized.

10.8 Safety Analyses

10.8.1 Treatment Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as an event that was not present prior to administration of the dose of study drug and present after the dose or if it represents the exacerbation of an event that was present prior to the dose.

Adverse events noted during the study will be coded to system organ classes (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The overall incidence of TEAEs will be classified by SOC and PT, and potentially summarized by groups based on baseline characteristics. Deaths, AE severity, seriousness, relationship to study drug will also be tabulated, potentially by groups based on baseline characteristics. If included, grouping based on baseline characteristics will be described in the SAP.

Ocular AEs will be presented separately for the study eye and the fellow eye.

10.8.2 Other Safety Assessments

Ophthalmology findings will also be summarized using descriptive statistics, frequencies, and percentages, and shifts from baseline, as appropriate. The number of subjects with a 10- and 15-letter decrease from baseline in BCVA will be tabulated.

10.9 Systemic Exposure Analyses

Systemic exposure will be estimated using standard methodology, if adequate serum concentrations of QR-421a are detected.

10.10 Efficacy Analyses

The efficacy evaluations will include evaluations of the endpoints listed in Section 4.1.

Descriptive statistics of clinical efficacy will be presented for study eye and fellow eye and will potentially be tabulated by groups based on baseline characteristics.

Further detail about the analysis and reporting of study data will be provided in the SAP.

10.11 Interim Analysis

Ongoing review of safety and efficacy data will be conducted to inform the program. Interim analyses may be performed, e.g., yearly, or at key time points during clinical development.

10.12 Subgroup Analyses

Exploratory analyses may be carried out for subgroups based on age, baseline visual acuity, and other factors identified in the SAP.

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Collection

The Investigator will prepare and maintain adequate and accurate source documents (including medical records) designed to record all observations and other pertinent data for each subject treated with the study treatment. Study center staff at each study center will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF. Subjects will not be identified by name in the study database or on any study documents to be collected by

the Sponsor (or designee) but will be identified by a study center number and subject number, which will be completed in the Screening and Enrollment Log. This number will be used for the duration of their participation in the study. The subject Screening number cannot be re-used if a subject withdraws consent or is a screening fail.

Study center staff will be trained and authorized to use the system in compliance with the Code of Federal Regulations (CFR) 21CFR Part 11, International Council for Harmonisation (ICH) - Good Clinical Practice (GCP) and local regulations, before recording data on eCRFs. All corrections to eCRFs will be made by authorized users, and the changes will be automatically logged in the audit trail of the system (time and date stamps and the user entering or updating data). Electronic CRFs should be completed for every subject screened or enrolled in the study. At the study's conclusion, a Portable Document Format file will be created for each study center containing their subjects' data submitted on eCRFs. A copy of the eCRF will remain at the study center at the completion of the study.

The Investigator is responsible for all information collected on subjects enrolled in this study and shall ensure that the eCRFs are accurate, complete, and completed in a timely fashion. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. The Investigator will ensure that the eCRFs are accurate, complete, and completed in a timely fashion. The Investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are retained according to storage guidelines (Section 13.4). Separate source records are required to support all eCRF entries. The eCRF is not to be used to document data without prior written or electronic records. The Investigator will electronically sign and date in the required places in the eCRF. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF and agrees with the content.

11.2 Data Quality Control

To ensure the quality of clinical data across all subjects and study centers, a clinical data management review will be performed on subject data. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and ICH GCP. To resolve any questions arising from the clinical data management review process, data queries will be sent to the study center. Corrections or updates to the data resulting from queries should be made on the eCRF. All changes will be automatically documented in the software's audit trail, including the reason for change.

11.3 Monitoring

A Sponsor representative (monitor) will contact the Investigator(s) at periodic intervals by telephone or on-site visit for the purpose of monitoring the facilities and assessing the progress of the study. Electronic CRFs and subject records will be reviewed at on-site visits at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy, and

consistency of the data, and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRF.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits, including delays in completing eCRFs, are resolved.

Monitoring of study center facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. Study drug dispensing and accountability will also be assessed.

11.4 Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/EC may perform audits or inspections at the study center, including source data verification. The purpose of an audit or inspection is to examine all study-related activities and documents systematically and independently, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at the study center.

12.0 ETHICAL AND REGULATORY OBLIGATIONS

12.1 Ethical Considerations

The Investigator agrees to conduct this study in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP. The Investigator will conduct all aspects of this study in compliance with the protocol, ICH GCP and applicable regulatory requirements.

12.2 Informed Consent

Before the start of required study procedures, the Investigator or his/her associate must obtain informed consent from each study subject in accordance with ICH GCP, and country authority requirements.

Age-appropriate assent and permission from a minor (12 to < 18 years) subject's parent or legal guardian is required for pediatric subjects. The subject must sign the current version of the written, IRB/EC-approved Informed Consent Form (ICF) in the presence of a witness and be given a copy. The Investigator will ensure that a copy of the signed consent is kept with the subject's records.

In accordance with ICH GCP and country authority requirements, an IRB/EC must review and approve this protocol and the ICF prior to initiation of the study.

12.3 Ethics and Regulatory Review

An IRB/EC should approve the final study protocol, including the final version of the ICF, assent forms and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable IRB/EC, and to the study center staff.

The opinion of the IRB/EC should be given in writing. The Investigator should submit the written approval to Sponsor before enrollment of any subject into the study.

The IRB/EC should approve all advertising used to recruit subjects for the study.

The Sponsor should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/EC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The Sponsor will handle the distribution of any of these documents to the national regulatory authorities.

The Sponsor will provide Regulatory Authorities, IRB/ECs and Investigators with safety updates/reports according to local requirements.

Each Investigator is responsible for providing the IRB/EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the Investigator so that he/she can meet these reporting requirements.

12.4 Subject Confidentiality

The Investigator and the Sponsor must ensure that the subject's confidentiality is maintained, in accordance with GCP and local regulations. On the eCRFs or other documents submitted to the Sponsor, subjects should be identified by their age and subject number only. Documents that are not for submission to the Sponsor (eg, signed ICF), should be kept in strict confidence by the Investigator.

The Investigator and the Sponsor will ensure that all clinical study information shall be recorded, processed, handled, and stored, in such a way that it can be accurately reported, interpreted, and verified while the confidentiality, integrity and availability of records and the personal data of the subjects remain protected in accordance with the applicable (local) laws on personal data

protection. Measures taken to ensure all the above include, but are not limited to, encryption, anonymization, multifactor authentication, Intrusion Protection, segregation of authentication.

In compliance with applicable regulations, it is required that the Investigator and institution permit authorized representatives of the Sponsor, the United States (US) Food and Drug Administration (FDA), other regulatory authorities (ie, European Union/European Economic Area member state, Q&A: Good clinical practice (GCP) | European Medicines Agency (europa.eu), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any or all records and reports that are important to the evaluation of this study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to the study-related records without violating the confidentiality of the subject.

The sponsor will notify the Member States concerned about a serious data security breach at the time of the breach without undue delay but not later than 7 days of becoming aware of that breach. Measures that will be implemented to mitigate the possible adverse effects of a serious data security breach include, but are not limited to, back-ups including remote location, high availability systems for critical environments, and a security incident response plan.

13.0 STUDY ADMINISTRATION

13.1 Investigator's Brochure

Before the study begins, the Investigator will receive the QR-421a IB describing all known nonclinical data, contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the IB will be amended or revised, and the Sponsor will provide the most current version to the Investigator.

13.2 Protocol Amendments

If there are any substantial changes to the study protocol, these changes will be documented in a protocol amendment and in a new version of the protocol. The Sponsor will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any ICF modifications to the IRB/EC, and approval must be obtained before the modifications are implemented. The Investigator must send a copy of the approval letter from the IRB/EC to the Sponsor for review. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to subjects without prior IRB/IEC approval/favorable opinion. In this case, as soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the sponsor, IRB/EC and if applicable the regulatory authority.

13.3 Study Termination

Both the Sponsor and the Investigator reserve the right to terminate the study according to the study contract. The Investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to the Sponsor.

If the Sponsor, Medical Monitor or designee, study center monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that a study center should be terminated, this action may be taken after appropriate consultation. Termination may occur in accordance with the clauses contained in the study center's executed clinical study agreement. The Sponsor reserves the right to discontinue the study prior to enrollment of the intended number of subjects but intends only to exercise this right for valid scientific reasons.

If the clinical development of QR-421a is discontinued, the Sponsor shall immediately inform all Investigators/institutions and regulatory authorities. Study termination and follow-up will be performed in compliance with the conditions set forth in the ICH Guidelines S7A (ICH 2000) and local regulatory requirements.

13.4 Study Documentation and Storage

The Sponsor will provide the Investigator with records of drug shipments, eCRFs, and other forms as necessary. The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include, but are not limited to:

- Subject files containing ICFs and supporting originals of source documentation.
- Study files containing the protocol with all amendments, IB, copies of pre-study documentation, and all correspondence to and from the IRB/EC, applicable country authorities, and the Sponsor.
- Records of drug accountability and all drug-related documentation.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Upon the request of the Sponsor, designees, or the regulatory authorities, the Investigator will make all study records available for inspection, including source documents. This information will be treated as confidential.

No study document is to be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

13.5 Use of Information

All personal data pertaining to the subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their month and year of birth and a subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing.

The sponsor will notify the Member States concerned about a serious data security breach at the time of the breach without undue delay but not later than 7 days of becoming aware of that breach. Measures that will be implemented to mitigate the possible adverse effects of a serious data security breach include, but are not limited to, back-ups including remote location, high availability systems for critical environments, and a security incident response plan.

The Investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the development of the study drug. This information may be disclosed to other clinical Investigators, to the US FDA, and to other government agencies.

Biological samples remaining after the tests described in this protocol are completed, may be used for additional research purposes. This additional research may be done by or on behalf of the Sponsor, to increase overall knowledge on QR-421a, and the effects of QR-421a on RP due to exon 13 mutations of the *USH2A* gene as well as the effect on other diseases. The samples may be stored or used for as long as they last or are needed for research.

The Sponsor will ensure that personal data transfers and bodily materials transfer comply with Data Protection Laws of the EU, ie, the General Data Protection Regulation 2016/679. To that end, all parties/vendors involved in this study will have been assessed and qualified by the Sponsor to ensure data privacy protection is at an adequate level. Appropriate contractual arrangements (Standard Contractual Clauses) will be in place and sufficient supplement technical measures will be implemented by the parties involved in the study.

13.6 End of Study and Final Report

Last Patient Last Visit defines the date that the last subject completed the study. The End of the Study is the date of the Last Patient Last Visit.

The Investigator or delegate must notify the IRB/EC upon study completion or termination in compliance with local regulations.

The Sponsor or its designee will provide a final report and/or synopsis to the Investigators, the IRB/EC and Regulatory Authorities in accordance with local requirements.

13.7 Financing and Insurance

Financing and Insurance are addressed separately in the Clinical Study Agreement.

13.8 Publication Policy

Publication policy is addressed separately in the Clinical Study Agreement.

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15.0 PROTOCOL SUMMARY OF CHANGES

16.0 APPENDICES

16.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Chemistry	**Hematology**	**Urinalysis (dipstick)**
Sodium	Hematocrit	Color and appearance
Potassium	Hemoglobin	Specific gravity
Chloride	Red blood cells	pH
Bicarbonate	White blood cells (WBCs)	Protein
Blood urea nitrogen (BUN)	Neutrophils	Glucose
Creatinine	Lymphocytes	Blood (erythrocytes)
Glucose	Monocytes	Leukocytes
Calcium	Eosinophils	Bilirubin
Phosphorus	Basophils	Ketones
Albumin	Platelets	Nitrite
Total protein		Urobilinogen
Alkaline phosphatase (ALP)		
Aspartate aminotransferase (AST)		
Alanine aminotransferase (ALT)		
Gamma-glutamyl transferase (ɣGT)		
Total and direct bilirubin		
Lactic dehydrogenase (LDH)		
Creatinine clearance (eGFR by CKD-EPI)*		
C-reactive protein (CRP)		
Other Tests		**Coagulation**
Pregnancy testing		INR Prothrombin time

* Estimated eGFR is to be calculated using the Chronic Kidney Disease Epidemiology Collaboration CKD-EPI Creatinine Equation 2009 calculation for adult subjects and Schwartz equation, according to the recommendation from National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases, for pediatric subjects