CLINICAL STUDY PROTOCOL

An Open-Label Extension Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of QR-110 in Subjects with Leber Congenital Amaurosis (LCA) due to the c.2991+1655A>G Mutation (p.Cys998x) in the *CEP290* Gene

Protocol No.	PQ-110-002
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Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands

INVESTIGATOR SIGNATURE PAGE

PRINCIPAL INVESTIGATOR COMMITMENT:

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.

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.

_____

Signature of Principal Investigator

_____

Printed Name of Principal Investigator

_____

Date

PROTOCOL APPROVAL PAGE

STUDY TITLE: An Open-Label Extension Study to Evaluate the Safety, Tolerability, Efficacy, and Pharmacokinetics of QR-110 in Subjects with Leber Congenital Amaurosis (LCA) due to the c.2991+1655A>G Mutation (p.Cys998x) in the *CEP290* Gene

I have read this protocol and agree that it contains all necessary information required to conduct the study.

_____ _____

Date

1.0 SYNOPSIS

Name of the Sponsor:	ProQR Therapeutics
Name of Investigational Product:	QR-110 Solution for Intravitreal Injection
Name of Active Ingredient:	QR-110
Title of Study:	An Open-Label, Extension Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of QR-110 in Subjects with Leber Congenital Amaurosis (LCA) due to the c.2991+1655A>G Mutation (p.Cys998X) in the *CEP290* Gene
Protocol number:	PQ-110-002
Study Centers:	3 centers
Phase of Development:	Phase 1b/2
Study Period:	Until provision of continued treatment by other means is available.
Duration of Subject Participation:	
Rationale:	Leber congenital amaurosis (LCA) is a severe inherited retinal degenerative disease resulting in blindness, often in early childhood. In subjects with LCA due to the p.Cys998X mutation in Centrosomal Protein of 290 kDa (*CEP290*), visual symptoms are usually detectable before 1 year of age and further deterioration over time has also been reported (den Hollander 2008; Yzer 2012). Patients show severe vision disturbances from an early age and slow progressive loss of remaining vision (Cideciyan 2007; Cideciyan 2011, Jacobson, 2017). There are currently no approved therapies for the treatment of LCA due to the p.Cys998X mutation in *CEP290* (subsequently referred to as the *CEP290* p.Cys998X mutation) and a large unmet medical need exists. The *CEP290* p.Cys998X mutation results in aberrant splicing of *CEP290* with mutant messenger ribonucleic acid (mRNA) and truncated protein production in affected individuals. Study drug QR-110 is a single-stranded, chemically modified, ribonucleic acid (RNA) oligonucleotide that is designed to correct aberrant splicing in *CEP290* gene, enabling production of fully functional RNA and protein. Subjects completing participation in study PQ-110-001 will be given the opportunity to enroll into the extension study for continued dosing if available data support current and/or future benefits for the subject. Study PQ-110-002 will provide long-term safety, tolerability, pharmacokinetic (PK), and efficacy data of QR-110.

Objectives	**Endpoints**
Primary • To evaluate long-term safety and tolerability of QR-110 administered via intravitreal (IVT) injection	Primary endpoints • Frequency and severity of ocular adverse events (AEs) • Frequency and severity of non-ocular AEs
Secondary • To evaluate long-term and sustained efficacy of QR-110 administered by IVT injection, as assessed by functional and structural outcome measures • To evaluate changes in Patient Reported Outcome (PROs) measures in subjects treated with QR-110 • To evaluate long-term serum pharmacokinetics (PK) of QR-110 administered by IVT injection	Secondary endpoints • Change in Best Corrected Visual Acuity (BCVA) • Change in Mobility course score (unilateral and binocular) • Change in photoreceptor outer segment layer thickness by Optical Coherence Tomography (OCT) (if applicable) • Change in Oculomotor Instability (OCI) • Change in Full-Field Stimulus Testing (FST) (blue and red stimuli; white at Investigator discretion) (thresholds) • Change in PROs, as measured by: o Visual Function Questionnaire-25 (VFQ-25) score (adult subjects), or o Cardiff Visual Ability Questionnaire for Children (CVAQC) score (pediatric subjects) • Change in Pupillary Light Reflex (PLR) (latency and amplitude) • Change in Near Infrared AutoFluorescence (NIRAF) • Pharmacokinetics: Characterize the PK profile of QR-110 in serum
Exploratory	Exploratory endpoints (at Investigator discretion)

Study Design:	PQ-110-002 study is an open-label, extension study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of QR-110 in subjects with LCA due to p.Cys998X in the *CEP290* gene. Subjects will be given the opportunity to enroll into this extension study for continued dosing if available data support current and/or future benefits for the subject. The Investigator, in consultation and agreement with the Medical Monitor, will decide on enrollment of each individual subject, as well as on dosing of the first treated eye and treatment initiation of the contralateral eye. 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. Dose modifications or modifications of the dosing interval will be considered on the basis of emerging safety and/or efficacy data and if it is anticipated to be in the best interest of the subject.

	The contralateral eye and the first treated eye will be injected 3 months apart. The injection interval of 3 months between both eyes will limit burden for the subjects, with a 3 month-visit frequency during the course of the study. This between-eye interval could be adapted if safety data are supportive, and for logistic reasons, and in agreement with the Medical Monitor. The same safety monitoring protocol and efficacy assessments will apply to both eyes. QR-110 will be administered via IVT injection in accordance with the procedures outlined by the American Academy of Ophthalmology (Avery 2014). Baseline functional and structural measurements for the first treated eye will be those from study PQ-110-001. Baseline functional and structural measurements for the contralateral eye will be those from the Screening /Day 1 visit of the current study.
Study Plan:	The Screening/Day 1 visit for this study should be the last visit (EOS visit) of study PQ-110-001, ie, all Screening/Day 1 assessments should take place during the EOS visit of study PQ-110-001. If these visits do not occur at the same time, a separate Screening/Day 1 visit should be performed as part of PQ-110-002. During the Screening/Day 1 visit, subjects will be assessed according to the eligibility criteria. Measures of visual function (including BCVA, FST, OCI, and mobility course), and retinal anatomy (OCT) will be assessed a minimum of 1 time prior to the subject receiving study drug. Any pre-dose assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator or if the assessment could not be completed. Additional assessments may be performed at Investigator discretion. Assessments can be completed over multiple days. The Investigator, in consultation with the Medical Monitor, will decide on subject's enrollment upon assessment of subject's benefit/risk. Any AE considered to be related to the study drug should be considered. 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 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 will continue to be followed for safety and efficacy for at least 3 months. 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 will be monitored in clinic for increases in intraocular pressure (IOP) and signs of intra-ocular inflammation and endophthalmitis during the post-injection period, ie, the day of the injection and on the day after injection (1 day post dose). The Day 7 post-dose visit will be a phone call from the site to the subject. All assessments will be performed on both eyes, even if the contralateral eye is not treated. The frequency of assessments is presented in the Schedule of Events More frequent evaluation may be undertaken for an individual subject to monitor safety and efficacy at the discretion of the Investigator. Data for all unscheduled visits should be recorded in the electronic case report form (eCRF). The Sponsor will perform safety and efficacy reviews on an ongoing basis.
Number of Subjects (planned):	Maximum of 11 subjects who have completed Study PQ-110-001.
Diagnosis and Main Criteria for Eligibility:	Inclusion Criteria: 1. Subjects who completed participation in the study PQ-110-001 and who may derive benefit from continued treatment with QR-110, as assessed by the Investigator, in consultation with the Medical Monitor (Section 4.2). 2. Persistence of detectable outer nuclear layer (ONL) in the area of the macula in the opinion of the Investigator, as determined by OCT. 3. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator. 4. An adult (≥ 18 years) willing and able to provide informed consent for participation OR a minor (6 to < 18 years) 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, and pediatric subjects able to provide age-appropriate assent for study participation. 5. 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, in the opinion of the Investigator 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, in the opinion of the Investigator. 6. Female subjects who have reached menarche and male subjects must either practice true abstinence in accordance with their preferred and usual lifestyle, or agree to use acceptable, highly effective methods of contraception for up to 6 months following their last dose QR-110. Acceptable methods of contraception are defined in the protocol. Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in the protocol (Section 6.2.3). 7. Adequate verbal communication as to allow assessment via mobility course, in the opinion of the Investigator.

	Exclusion Criteria: 8. Any contraindication to IVT injection according to the Investigator's clinical judgment and international guidelines (Avery 2014). 9. Safety issue during study PQ-110-001 that may compromise subject safety when continued dosing, as determined by the Investigator, and in consultation with the Medical Monitor. • Subjects with existing safety events from study PQ-110-001 may be included as determined by the Investigator and in consultation with the Medical Monitor. 10. Any ocular or systemic disease or condition (including medications and laboratory test abnormalities) that could compromise subject safety or interfere with assessment of efficacy and safety, as determined by the Investigator and in consultation with the Medical Monitor. 11. Pregnant or breast-feeding female.
Study Drug, Dosage, and Mode of Administration:	QR-110 Solution for IVT Injection, • First treated eye: maintenance dose of 80 µg every 6 months • Contralateral eye: 160 µg loading dose followed by 80 µg maintenance dose, every 6 months Both eyes will be injected 3 months apart.
Duration of Treatment:	
Reference Therapy, Dosage, and Mode of Administration:	Not applicable.
Pharmacokinetics:	Blood samples will be collected at predefined time points for the presence of QR-110
Statistical Methods:	Analyses will generally be descriptive in nature and will focus on data collected during this study. Baseline functional and structural measurements for the first treated eye will be those from study PQ-110-001. Baseline functional and structural measurements for the contralateral eye will be collected during the Screening visit and will serve as a control. The incidence of AEs and changes in clinical laboratory assessments will be summarized for subjects by dose group, age category (pediatrics and adults), and for the study population. Ocular AEs will be summarized for all subjects using descriptive statistics for each eye. Efficacy endpoints will be summarized for all subjects using descriptive statistics for each eye. For all the relevant analyses, the data may be summarized for subjects by dose group, age category, genetic status, and severity of the disease (BCVA and other visual function and/or functional vision parameters). Summary statistics for other safety, efficacy, and PK endpoints will be presented. Further details will be provided in the Statistical Analysis Plan (SAP).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
λz	elimination rate constant
ɣGT	gamma-glutamyl transferase
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AON	antisense oligonucleotide
AREDS	age-related eye diseases study
ARLNS	age-related eye diseases study clinical lens grading system
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the curve 0 hour to infinity
$AUC_{0-tlast}$	area under the curve 0 hour to time of the last measurable concentration
BCVA	Best Corrected Visual Acuity
BRVT	Berkeley Rudimentary Vision Test
BUN	blood urea nitrogen
CBC	complete blood count
CEP290	Centrosomal Protein of 290 kDa
CF	counting fingers
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
C_{last}	last observed concentration
C_{max}	maximum concentration
C_0	trough value
CSR	clinical study report
CVAQC	Cardiff Visual Ability Questionnaire for Children
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study

Abbreviation	Definition
ESE	exonic splicing enhancer
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FST	Full-field Stimulus Testing (also, Full-field Stimulus Threshold Testing or Full-field Scotopic Threshold Testing)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HM	hand motion
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
INR	international normalized ratio
IOP	intraocular pressure
iPSC	induced pluripotent stem cells
IRB	Institutional Review Board
IVT	intravitreal
LCA	Leber congenital amaurosis
LDH	lactic dehydrogenase
LLOQ	lower limit of quantification
LogMAR	Logarithm of the Minimum Angle of Resolution
LP	light perception
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NEHD	normalized equivalent human dose
NIDDK	National Institute of Diabetes and Digestive Kidney Disease
NIH	National Institute of Health
NIRAF	near infrared autofluorescence
OCI	oculomotor instability
OCT	optical coherence tomography
ONL	outer nuclear layer
PBS	Phosphate-buffered saline

Abbreviation	Definition
p.Cys998X	C.2991+1655A>G mutation in the *CEP290* gene
PD	pharmacodynamic
PK	pharmacokinetic
PLR	pupillary light reflex
PRO	patient reported outcome
ProQR	ProQR Therapeutics
PT	preferred term
RNA	ribonucleic acid
SAE	serious adverse event
SEM	standard error of mean
SAP	statistical analysis plan
SOC	system organ class
SOE	schedule of events
SOP	standard operating procedure
SUN	Standardization of Uveitis Nomenclature
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TLF	table, listing, and figure
$T_{1/2}$	terminal half-life
T_{max}	time of maximum concentration
ULN	upper limit of normal
US	United States
V_d	volume of distribution
VF	visual field
VFQ-25	Visual Function Questionnaire-25
WOCBP	women of childbearing potential

2.0 INTRODUCTION

ProQR Therapeutics (ProQR) is developing an antisense oligonucleotide (AON) product, QR-110, for the treatment of patients with Leber congenital amaurosis (LCA) due to the c.2991 +1655A>G mutation (p.Cys998X or IVS26+1655A>G) in the Centrosomal Protein of 290kDa (*CEP290*) gene. Leber congenital amaurosis is a severe inherited retinal degenerative disease resulting in blindness, often in early childhood. In patients with LCA due to the p.Cys998X mutation in the *CEP290* gene (subsequently referred to as *CEP290* p.Cys998X mutation), visual symptoms are usually detectable before 1 year of age and further deterioration over time has also been reported (den Hollander 2008, Yzer 2012). Patients show severe vision disturbances from an early age and slow progressive loss of remaining vision (Cideciyan 2007, Cideciyan 2011, McAnany 2013, Jacobson 2017). There are currently no approved therapies for the treatment of LCA due to the *CEP290* p.Cys998X mutation and a large unmet medical need exists. The primary goal of the development plan for QR-110 is to provide a treatment to overcome the genetic defect in patients with at least one *CEP290* allele containing the *CEP290* p.Cys998X mutation, resulting in functional vision restoration or preservation. The intended route of administration is intravitreal (IVT) injection.

2.1 Leber Congenital Amaurosis

Leber congenital amaurosis is a non-syndromic retinopathy that affects both cone and rod photoreceptor cells of the retina. It is a rare autosomal recessive disorder, reported to be the most severe and one of the earliest onset forms of vision loss in children, with detection of disease symptoms as early as the first year of life. The symptoms and signs include severe and early vision loss, sensory nystagmus (involuntary eye movements), abnormalities of pupil reactions, oculo-digital sign, and nondetectable photoreceptor electrical signals on electroretinogram (ERG). There are approximately 20 genes identified to date in which mutations are causative for LCA (den Hollander 2008, Estrada-Cuzcano 2011, Kmoch 2015), and the LCA classification is based on the disease causing gene. The most frequently mutated LCA gene is *CEP290*, with mutations accounting for about 15% to 30% of LCA cases (Coppieters 2010, den Hollander 2008, den Hollander 2006, Perrault 2007, Stone 2007).

The *CEP290* gene is located on the long (Q) arm of chromosome 12 and codes for *CEP290* protein, which has an important role in centrosome and cilia development. The most frequently occurring *CEP290* mutation associated with retinal dystrophy in Caucasians, especially in European countries and the United States (US), is a change in intron 26 of the *CEP290* gene (p.Cys998X) (Stone 2007, den Hollander 2006, Perrault 2007, Littink 2010). This mutation creates a cryptic splice donor site in intron 26, which results in the inclusion of an aberrant exon (exon-X) of 128 bases in the mutant *CEP290* messenger ribonucleic acid (mRNA). This cryptic exon introduces a premature stop codon, predicted to render *CEP290* a truncated protein. The mutation has been found in homozygosity or compound heterozygosity in patients with *CEP290* LCA (Cideciyan 2007, den Hollander 2006, Perrault 2007). Both the homozygous and heterozygous genotypes result in a similar clinical presentation. The *CEP290* p.Cys998X

mutation appears to be hypomorphic in nature, with wild-type transcripts present in peripheral tissues, explaining the non-syndromic nature of the *CEP290* p.Cys998X mutation (Parfitt 2016).

2.2 QR-110 for the Treatment of Leber Congenital Amaurosis due to *CEP290* p.Cys998X Mutation

The primary goal of the development plan for study drug QR-110 is to provide a treatment to overcome the genetic defect in patients with at least 1 *CEP290* allele containing the p.Cys998X mutation.

2.2.1 Nonclinical Experience

These studies are summarized in the QR-110 Investigator's Brochure (IB), Nonclinical Studies.

2.2.2 Clinical Experience

The clinical development program started in the second half of 2017 with the first-in-human (FIH) clinical study (PQ-110-001), a Phase 1b/2, open-label, multiple-dose, dose-escalation to evaluate the safety and tolerability of QR-110. Following individual reports of efficacy an interim analysis was performed in August 2018. Available safety and efficacy data from Study PQ-110-001 support the therapeutic potential observed in the nonclinical studies. Reference is made to the IB for further details.

2.3 Study Rationale

This extension study allows subjects completing study PQ-110-001, who derive benefit from QR-110 treatment, to continue to receive treatment and to observe the long-term safety, tolerability, PK, and efficacy of treatment with QR-110. Additionally, this extension study allows for the treatment of the previously untreated contralateral eye.

2.3.1 Dose Selection

Each subject will receive a maintenance dose of 80 µg at 6-monthly intervals in the first treated eye. Treatment of the contralateral eye will begin with a loading dose of 160 µg and is followed by a maintenance dose of 80 µg at 6-monthly intervals. The contralateral eye and the first treated eye will be injected 3 months apart. Dose modifications or modifications of the dosing interval will be considered on the basis of emerging safety and/or efficacy data and if it is anticipated to be in the best interest of the subject.

Details on the dose selection are provided in the QR-110 IB.

Minimizing the number of injections is important for safety reasons and to decrease subject burden. Based on observed durability of responses between injections in Study PQ-110-001, longer dosing intervals of up to 6 months will be explored in this study.

2.4 Study Population

Subjects who completed study PQ-110-001, met eligibility requirements, and for whom the assessment of benefit/risk is positive may participate in the study.

2.4.1 Pediatric Considerations

In accordance with best practices, the parent or legal representative of a participating pediatric subject must be informed as to procedures that are part of usual care and those specific to participation in this clinical study. Age-appropriate explanations of procedures should be given to all pediatric subjects. Investigators, staff, and facilities should be experienced in the care of pediatric subjects, in order to minimize pain, distress and fear. Separation of the pediatric subject from their parent or legal representative should be minimized and when necessary, the pediatric subject should be accompanied by a study staff member. Pain should be minimized (eg, use of indwelling catheters for blood draws or use of topical anesthetic agents), in accordance with local institutional practices (Directive 2001/20/EC, Regulation 536/2014).

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate long-term safety and tolerability of QR-110 administered via IVT injection.

3.2 Secondary Objectives

The secondary objectives of the study are to:

- Evaluate long-term and sustained efficacy of QR-110 administered by IVT injection, as assessed by functional and structural outcome measures
- Evaluate changes in Patient Reported Outcome (PROs) measures in subjects treated with QR-110
- Evaluate long-term serum PK of QR-110 administered by IVT injection

3.3 Exploratory Objectives

4.0 STUDY OVERVIEW

4.1 Criteria for Evaluation

4.1.1 Primary Endpoint

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

4.1.2 Secondary Endpoints

- Change in BCVA
- Change in Mobility course score (unilateral and binocular)
- Change in photoreceptor outer segment layer thickness by optical coherence tomography (OCT) (if applicable)
- Change in OCI
- Change in Full-FST (blue and red stimuli; white at Investigator discretion) (thresholds)
- Change in PROs, as measured by:
  - Visual Function Questionnaire-25 (VFQ-25) score (adult subjects), or
  - Cardiff Visual Ability Questionnaire for Children (CVAQC) score (pediatric subjects)
- Change in Pupillary Light Reflex (PLR) (latency and amplitude)
- Change in Near Infrared AutoFluorescence (NIRAF)
- Pharmacokinetics: Characterize the PK profile of QR-110 in serum

4.1.3 Exploratory Endpoints (at Investigator Discretion)

4.2 Study Design

PQ-110-002 study is an open-label extension study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of QR-110 in subjects with LCA due to c.2991+1655A>G mutation (p.Cys998X) in the *CEP290* gene.

Subjects will be given the opportunity to enroll into the extension phase study PQ-110-002 for continued dosing if available data support current and/or future benefits for the subject from QR-110 treatment. The decision will be based on the assessment of individual subject's benefit/risk based on individual data and data from QR-110 clinical studies. The Investigator, in consultation with the Medical Monitor, will decide on enrollment of each individual subject, as well as on dosing of the first treated eye and treatment initiation of the contralateral eye. 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.

Dose modifications or modifications of the dosing interval will be considered on the basis of emerging safety and/or efficacy data and if it is anticipated to be in the best interest of the subject.

The contralateral eye and the first treated eye will be injected 3 months apart. The injection interval of 3 months between both eyes allows thorough safety evaluation and will decrease subject burden, with a 3 month-visit frequency during the course of the study. This between-eye interval could be adapted if safety data are supportive, and for logistic reasons, and in agreement with the Medical Monitor. The same safety monitoring protocol and efficacy assessments will apply to both eyes.

QR-110 will be administered via IVT injection in accordance with the procedures outlined by the American Academy of Ophthalmology (Avery 2014).

A program-specific review of safety, which may include independent experts, will be in place to assess emerging data from clinical studies on an ongoing basis.

Baseline functional and structural measurements for the first treated eye will be those from study PQ-110-001. Baseline functional and structural measurements for the contralateral eye will be those from the Screening/Day 1 visit of the current study which is the last visit of study PQ-110-001 (see Section 4.2.1.1).

4.2.1 Study Plan

4.2.1.1 Screening/ Day 1

The Screening/Day 1 visit for this study should be the last visit (EOS visit) of study PQ-110-001, ie, all Screening/Day 1 assessments should take place during the EOS visit of study PQ-110-001. If these visits do not occur at the same time, a separate Screening/Day 1 visit should be

performed as part of PQ-110-002 ~~(Appendix 1).~~ During the Screening/Day 1 visit, subjects will be assessed according to the eligibility criteria.

Measures of visual function (including BCVA, FST, OCI, and mobility course), and retinal anatomy (OCT) will be assessed a minimum of 1 time prior to the subject receiving study drug. Any pre-dose assessment may be repeated if the results are considered unreliable or of unacceptable quality by the Investigator or if the assessment could not be completed. Additional assessments may be performed at Investigator discretion.

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

The Investigator, in consultation 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.

Adverse events considered to be related to the study drug should be taken into account in the benefit/risk assessment.

See Section 7.0 for more details on the screening process.

4.2.1.2 Study Drug Administration

Subjects will receive study drug via unilateral IVT injection in accordance with the procedures outlined by the current international guidelines (Avery 2014) in their first treated eye and in the contralateral (previously untreated) eye and will be assessed for safety and tolerability at follow-up visits.

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. Subjects who discontinue study drug will continue to be followed for safety and efficacy for at least 3 months. 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.

Specific study drug administration procedures can be found in the Study Reference Manual.

4.2.1.3 Assessment and Follow-up

Subjects will be monitored in clinic for increases in intraocular pressure (IOP) and signs of intra-ocular inflammation and endophthalmitis during the post-injection period, ie, the day of the injection, and on the day after injection (1-day post-dose). The Day 7 post-dose visit will be a phone call from the site to the subject. If no dosing occurs at a visit; the +1D post dose visit and the +7D post dose phone call may be skipped; at the discretion of the Investigator.

All assessments will be performed on both eyes, even if the contralateral eye is not treated. The frequency of 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 and efficacy at the discretion of the Investigator. Data for all unscheduled visits should be recorded in the electronic case report form (eCRF). The Sponsor will perform safety and efficacy reviews on an ongoing basis.

Efficacy assessments will be performed according to the SOE

4.2.2 Stopping Criteria

The Investigator or the Medical Monitor may stop treatment for an individual subject due to an AE (Section 9.0). 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-110 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 will be encouraged to remain in the study for observation for at least 3 months post last dose.

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 decide to stop treatment for an individual subject due to an AE.

4.2.3 Subject Withdrawal

Subjects are free to withdraw from the study at any time (ie, discontinue study drug and assessments), without prejudice to further treatment. 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.

4.2.4 Discontinuation of the Study

The Medical Monitor will evaluate the safety and tolerability data as described in Section 4.2.2 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

A maximum of 11 subjects who have completed Study PQ-110-001, meet all eligibility requirements, and for whom the assessment of benefit/risk is positive are eligible to participate in this extension study.

5.2 Selection of Subjects

Subjects will be evaluated against all assessments of eligibility criteria as presented in the SOE Results of assessments for all eligibility criteria must be available and reviewed prior to the subject's first dose of study drug in this extension study.

5.3 Eligibility Criteria

5.3.1 Inclusion Criteria

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

1. Subjects who completed participation in study PQ-110-001 and who may derive benefit from continued treatment with QR-110, as assessed by the Investigator, in consultation with the Medical Monitor (Section 4.2).
2. Persistence of detectable ONL in the area of the macula in the opinion of the Investigator, as determined by OCT.
3. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator.
4. An adult (≥ 18 years) willing and able to provide informed consent for participation
   -OR-
   a minor (6 to < 18 years) 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 and pediatric subjects able to provide age appropriate assent for study participation.
5. 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, in the opinion of the Investigator
   -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, in the opinion of the Investigator.

6. Female subjects who have reached menarche and male subjects must either practice true abstinence in accordance with their preferred and usual lifestyle, or agree to use acceptable, highly effective methods of contraception for up to 6 months following their last dose of QR-110. Acceptable methods of contraception are defined in the protocol. Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in the protocol (Section 6.2.3).
7. Adequate verbal communication as to allow assessment via mobility course, in the opinion of the Investigator.

No waivers to the inclusion criteria are permitted.

5.3.2 Exclusion Criteria

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

1. Any contraindication to IVT injection according to the Investigator's clinical judgment and international guidelines (Avery 2014)
2. Safety issue during study PQ-110-001 that may compromise subject safety when continued dosing, as assessed by the Investigator, in consultation with the Medical Monitor.
3. Any ocular or systemic disease or condition (including medications and laboratory test abnormalities) that could compromise subject safety or interfere with assessment of efficacy and safety, as determined by the Investigator and in consultation with the Medical Monitor.
    - Subjects with existing safety events from study PQ-110-001 may be included as determined by the Investigator and in consultation with the Medical Monitor.
4. Pregnant or breast-feeding female.

6.0 STUDY DRUG AND CONCOMITANT THERAPIES

6.1 Study Drug

6.1.1 Study Drug Description and Supply

The QR-110 study drug is a solution for IVT injection.

The QR-110 study drug is supplied in glass vials with rubber stoppers, aluminum seal, and white flip-off cap. Vials are individually packed in cartons. Vials and cartons are labelled in compliance with local regulatory requirements.

All vials are sterile and for single use.

6.1.2 Placebo

No placebo is used.

6.1.3 Study Drug Shipment and Storage

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

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. Used vials should be retained for drug accountability by the Sponsor representative (monitor), unless prohibited by local procedures, in which case an alternative drug accountability process will be agreed upon with the Sponsor. Additional details on study drug handling are provided in the Pharmacy Manual and the Study Reference Manual.

Forms are provided to facilitate the inventory control. These forms must be used unless the Investigator has previously established a system that complies with local regulations and is approved by the Sponsor. The study drug must be dispensed only at the institution(s) specified on form Food and Drug Administration (FDA) 1572 or Statement of Investigator (as applicable).

Upon completion or termination of the study and after inventory by a Sponsor representative (monitor), it will be determined if unopened study drug vials are to be sent to the Sponsor in the original containers or are to be destroyed on site.

6.1.5 Dosage and Administration

Subjects will receive study drug with a 6-month dosing interval. Dose level or interval modifications may be considered on the basis of emerging safety and efficacy data from any QR-110 studies if this is anticipated to be in the best interest of the subject.

QR 110 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 according to the Pharmacy Manual for each administration.

Subjects will receive study drug by IVT injection. 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.

6.2 Concomitant Medications and Ancillary Therapy

6.2.1 Permitted Concomitant Medications

The medications usually used in ophthalmology care are permitted, including but not limited to: topical anesthetic agents, carbonic anhydrase inhibitors (intravenous, oral, topical), beta blocker ophthalmic solutions, prostaglandin analog ophthalmic solutions, ophthalmic solutions/gels of corticosteroids, antibiotics and antiseptics, topical agents for pupillary dilatation, and anti-allergic ophthalmic solutions, in accordance with the approved label or Summary of Product Characteristics of the products.

The concomitant medications recommended for IVT injection in the most recent guidelines (Avery 2014) are detailed in the Study Reference Manual.

6.2.2 Prohibited Concomitant Medications

The use of any investigational drug (other than QR-110) or device within 90 days or 5 half-lives of the drug at Day 1, whichever is longer, or plans to participate in another investigational study during the PQ-110-002 study period is prohibited. 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.

6.2.3 Adequate Forms of Birth Control

Female subjects who have reached menarche and male subjects must either practice true abstinence in accordance with their preferred and usual lifestyle, or agree to use acceptable,

highly effective methods of contraception

Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in the protocol.

Double barrier methods (a combination of condom with cap, diaphragm, or sponge with spermicide) are not considered highly effective. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Highly effective methods of birth control include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progesterone-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

Birth control measures must be employed during the time of participation (beginning at the Screening/Day 1 visit) in this study.

A man is considered fertile unless permanently sterile by bilateral orchidectomy or has undergone vasectomy and received medical assessment of surgical success.

7.0 STUDY VISITS

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

7.1 Visit and Assessment Windows

The timing of assessments, procedures, and sample collections are indicated in the SOE

Study center phone calls to the subjects will occur 7 days post-IVT injection, ±3 days. Study visits will occur every 3 months. If no dosing occurs, the phone call visits may be skipped at the discretion of the Investigator.

The Screening/ Day 1 visit should be the last visit of study PQ-110-00, ie, all Screening/Day 1 assessments should take place during the EOS visit of study PQ-110-001. If these visits do not occur at the same time, a separate Screening/Day 1 visit should be performed as part of PQ-110-002.

At the Screening/Day 1 visit, subjects will be assessed according to the eligibility criteria and specified assessments conducted, as presented in the SOE . For all subjects, assessments should be conducted in a stepwise manner so that eligibility is confirmed first with less intensive assessments. More intensive assessments or any assessments requiring sedation or anesthesia for a specific subject are to be conducted once eligibility by other criteria have been confirmed to minimize risk.

Assessments can be completed over multiple days.

7.2 Dosing and Follow-up Visits

Dosing visits occur on Day 1 for the contralateral eye and then every 6 months. Dosing visits for the previously (first) treated eye will occur 3 months after the dosing visit for the contralateral eye and then every 6 months.

This between-eye interval could be adapted in agreement with the Medical Monitor if safety data are supportive, and for logistic reasons.

Study drug will be administered by qualified ophthalmologists via IVT injection. If sedation or anesthesia is performed during the administration of the IVT injection, general health monitoring should be provided by the study anesthesiologist pre and post sedation/anesthesia, according to local institutional guidelines. Subjects should be monitored for increases in IOP and signs of inflammation and endophthalmitis during the post-injection period.

Study center phone calls to the subjects will occur 7 days post-IVT injection, ±3 days.

All follow-up study visits, assessments and procedures should be completed as indicated in the SOE However, if no dosing occurs at a visit; the +1D post dose visit and the +7D post dose phone call may be skipped at the discretion of the Investigator.

7.3 End of Study Visit

The End of Study (EOS) visit occurs 3 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 3 months post last dose.

8.0 STUDY ASSESSMENT PROCEDURES

Safety parameters will be assessed by monitoring AEs, vital signs, physical examinations, ophthalmic exams, OCTs, infrared imaging, electrocardiograms (ECGs), and laboratory data (serum chemistry, hematology, and inflammatory markers). Assessments will be conducted as indicated on 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.

8.2 Vital Signs

Blood pressure, heart rate and oral temperature will be measured after the subject has been resting in a seated position for a minimum of 5 minutes.

8.3 Laboratory Evaluations

All laboratory evaluations will be conducted at a central laboratory. Reference ranges for all laboratory parameters are provided in the Laboratory Manual.

A list of all clinical laboratory evaluations is presented in Appendix 2.

Serum chemistries will include sodium, potassium, chloride, bicarbonate, uremia or blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, albumin, total protein, ALP, AST, ALT, gamma-glutamyl transferase (ɣGT), total and direct bilirubin, uric acid, lactic dehydrogenase (LDH), creatinine clearance (estimated glomerular filtration rate [eGFR]), and international normalized ratio (INR). Estimated GFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation 2009 calculation for adult subjects and the Schwartz equation, according to the recommendation from National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), for pediatric subjects.

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

For female subjects of childbearing potential, a urine pregnancy test is recommended at any visit that may warrant a pregnancy test.

Eligibility of the subject to participate in the extension study is based in part on safety signals that may be indicated by laboratory values.

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 indicate safety concerns should be discussed with the Medical Monitor prior to subject inclusion.

8.4 Immunogenicity

Blood samples will be obtained to monitor for possible development of antibodies to QR-110, as indicated per the SOE

8.7 Pharmacokinetic Evaluations

Blood samples will be obtained from all subjects to assess QR-110 PK parameters (area under the curve from 0 hour to infinity [$AUC_{0-\infty}$], area under the curve from 0 hour to time of the last measurable concentration BCVA [$AUC_{0-tlast}$], maximum concentration (C_{max}), trough value [C_0], time to maximum concentration [T_{max}], terminal half-life [$T_{1/2}$], clearance [CL], volume of distribution [V_d]) as indicated per the SOE PK parameters will only be evaluated if measurable serum levels are obtained.

8.8 Electrocardiogram

Twelve-lead ECG will be obtained as indicated per the SOE
Electrocardiograms should be done in triplicate after the subject has been resting comfortably in a supine position for a minimum of 8 minutes. The mean of triplicate results will be captured in the eCRF.

A repeat of ECGs (in triplicate) is permitted to confirm potentially spurious results, at the discretion of the Investigator. Repeat analysis results should be discussed with the Medical Monitor. Details on the conduct of ECGs is provided in the Study Reference Manual.

8.9 Physical Examination

Complete and symptom-directed physical examinations (urogenital exams not required) will be performed as indicated per the SOE

8.10 Ophthalmic Exams

Ophthalmic examinations will be performed per the SOE The ophthalmic exam is comprised of: anterior segment examination, including grading of anterior chamber inflammation according to the Standardization of Uveitis Nomenclature (SUN) Working Group Grading Scheme for Anterior Chamber Flare; OCI; FST; IOP; clinical lens grading using the Age-Related Eye Diseases Study (AREDS) Clinical Lens Grading System (ARLNS); posterior segment/fundus examination including grading inflammation in the vitreous using the NIH Grading Scale for Vitreous Haze.

Best Corrected Visual Acuity will also be assessed at specified time points as indicated per the SOE The BCVA will be assessed using the BRVT and the ETDRS acuity test. The procedures for ophthalmic exams are outlined in the Study Reference Manual.

8.11 Optical Coherence Tomography

Changes in OCT findings are of relevance to the safety profile of QR-110. Optical Coherence Tomography images will be evaluated for changes in the remaining volume of ONL and foveal thickness as safety parameters. All OCT scans should be performed in accordance with the procedures outlined in the Image Acquisition and Submission Protocol.

The Medical Monitor should review all OCT scans, with particular attention to identifying changes including, remaining volume of ONL, foveal thickness, appearance of cystoid macular edema, or macular edema as compared to baseline.

8.12 Efficacy Assessments

Efficacy assessments include BCVA, mobility course, FST, OCI, PROs, PLR, and NIRAF.

If possible, photoreceptor outer segment layer thickness will be calculated from OCT images as a secondary efficacy parameter. This assessment will be conducted for those subjects for whom high quality imaging to evaluate this parameter can be obtained, as determined by the Investigator.

Subjects' assessment of the impact of their visual disability on general health-related outcomes as well as specific vision-related outcomes of daily living will be assessed for adult subjects by the VFQ-25 and for pediatric subjects by the CVAQC.

Secondary efficacy response criteria will be obtained as indicated per the SOE

9.0 ASSESSMENT OF SAFETY OR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All subjects who receive study drug 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.

9.1 Review of Safety Data

A program-specific review of safety data, which may include independent experts, will be in place to assess emerging data from clinical studies on an ongoing basis.

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

9.2.1 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 physical examination, 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 9.4.1)
- Adverse events not previously observed in the subject that emerge during the protocol-specified AE reporting period (as specified in Section 9.4.1)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as IVT injections)
- Adverse events that occur prior to study treatment that are related to a protocol-mandated intervention (eg, invasive procedures such as blood draws, anesthesia prior to IVT injection)

9.2.2 Serious Adverse Events

A serious adverse event (SAE) is any AE that suggests a significant hazard, contraindication, side effect, or precaution regardless of the relationship to study drug. An SAE is any AE that 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 hospitalization for planned post dose sample collections
- Persistent or significant disability/incapacity (ie, 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.

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) (Section 9.3.1). "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.

9.2.3 Suspected Unexpected Serious Adverse Reaction Definition

A suspected unexpected serious adverse reaction (SUSAR) is a suspected unexpected serious adverse reaction. In order to be qualified as a 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 (ie, 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.

9.2.4 Adverse Events of Special Interest

The following are considered AEs of special interest, based on the route of administration and safety profile for QR-110.

9.3 Assessment of Adverse Events

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

9.3.1 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 9.2.2, note the distinction between the severity and the seriousness of AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above in Section 9.2.2.

9.3.2 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 (eg, 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 (eg, cancer diagnosed 2 days after first dose of study drug).

Possibly Related: An AE that follows a reasonable temporal sequence from administration of the study drug, follows a known or expected response pattern to the study drug, but that could readily have been produced by a number of other factors.

Probably Related: An AE that is clearly related to the study drug or its administration (ie, 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 is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject’s clinical state).

Definitely Related: The AE is clearly related to the study drug; a re-challenge confirms the association (not required or desirable in some circumstances but provides strong evidence when it happens).

For all AEs and SAEs, Investigators will make separate assessments of causality about the relationship of the event to study drug and to drug administration (ie, 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, and SAE 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.

9.3.3 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).

9.4 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, and/or SAE form, and reported to the Sponsor in accordance with protocol instructions.

9.4.1 Adverse Event Reporting Period

Any event/condition noted once the subject receives their first dose of study drug in the contralateral eye will be captured as an AE.

In the first treated eye all events/conditions will be captured as an AE as treatment continues from study PQ-110-001.

All AEs and SAEs regardless of attribution will be collected until at least 3 months 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.

Adverse events and SAEs related to study drug that persist > 3 months after the last study drug dose should be followed until resolution or until they return to baseline, stabilize, the subject is lost to follow-up, or it has been determined that the study drug or participation is not the cause of the AE/SAE.

Resolution of AEs and SAEs (with dates) should be documented on the AE eCRF and SAE 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).

9.4.2 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?*"

Age-appropriate non-directive questions should be employed for eliciting AEs from pediatric subjects. Non-directive questions may also be used to elicit AEs from parents/caregivers of pediatric subjects, at the discretion of the Investigator.

9.4.3 Recording Adverse and Serious Adverse Events

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

9.4.3.1 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, 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, on the SAE form.

9.4.3.2 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.

9.4.3.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs on the eCRF and SAE 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 and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

9.4.3.4 Deaths

All deaths that occur during the protocol-specified AE reporting period (Section 9.4.1), regardless of attribution, will be recorded on the AE eCRF and SAE 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 and SAE form.

9.4.3.5 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 and Surgical 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 and SAE form (if applicable), it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (eg, "more frequent headaches").

9.4.3.6 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.

9.4.3.7 Pregnancy

If a female subject or a female partner of a male subject becomes pregnant while the female subject or the male partner is receiving study drug
a Pregnancy Report form should be completed and faxed to the Drug Safety designee within 24 hours of learning of the pregnancy, using the fax numbers listed in the Study Reference Manual.

Abortion, whether therapeutic or spontaneous, will be reported on a Pregnancy Report form and faxed to the Sponsor according to the instructions in the Study Reference Manual. If the abortion meets seriousness criteria (Section 9.2.2, Serious Adverse Event Definition), this information will be captured on the AE eCRF and SAE form.

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.

9.4.3.8 Overdose Reporting

Overdoses must be reported to the Sponsor on an AE eCRF and an SAE form 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 overdose information will be provided by the Sponsor at the time of notification.

9.5 Serious Adverse Events Notification

For all SAEs, regardless of suspected causality, an SAE form must be completed (or faxed if using paper form) within 24 hours of discovery of the event to:

DRUG SAFETY

Fax toll-free: See Study Reference Manual for Fax Number

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 toll-free: See Study Reference Manual for Phone Number

followed by submission of written case details on an SAE 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 SAE 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 SAE 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 SAE form.
- All SAEs must be reported to the IRB/EC, if applicable. See the International Council for Harmonization (ICH) Good Clinical Practice (GCP) E6, Section 4.11.1 (ICH GCP 2016).

9.6 Expedited Reporting of Suspected Unexpected Serious Adverse Reactions

- The Sponsor or its designee is responsible for notifying the study centers of all expedited SAEs (ie, 7/15 Day SUSARs) 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 local requirements. All SUSARs will be reported to the Regulatory Authorities as per local requirements.
- 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, the Detailed Guidance CT-3 (2011/C 172/01), and Regulation 536/2014.

10.0 STATISTICAL METHODOLOGY

10.1 General Considerations

Analyses will generally be descriptive in nature and will focus on data collected during this study. Baseline functional and structural measurements for the first treated eye will be those from study PQ-110-001. Baseline functional and structural measurements for the contralateral eye will be collected during the Screening visit. The incidence of AEs and changes in clinical laboratory assessments will be summarized for subjects by dose group, age category (pediatrics and adults), and for the study population. Efficacy endpoints will be summarized for all subjects using descriptive statistics for each eye. For all the relevant analyses, the data may be summarized for subjects by dose group, age category, genetic status, and severity of disease (BCVA and other visual function and/or functional vision parameters). An analysis by 3- or 6-month intervals may also be performed. Summary statistics for other safety, efficacy, and PK endpoints will be presented. Further details will be provided in the Statistical Analysis Plan (SAP).

A comprehensive SAP will specify the statistical methodology, 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-110 unless obviously unrelated. As an open-label extension 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. Additionally, no adjustment for multiplicity will be done due to 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 (SOPs) of the Sponsor.

10.2 Determination of Sample Size

The sample size is determined by the number of subjects completing study PQ-110-001 who meet the inclusion and exclusion criteria and provide informed consent.

10.2.1 Randomization and Blinding

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

10.2.2 Replacement of Subjects

Not applicable as this is an extension study.

10.3 Analysis of Populations

Safety Population: the population for safety analysis will consist of all subjects who receive any QR-110 or pre-medications required for the study.

Efficacy Evaluable Population: the population for efficacy (clinical activity) analysis will consist of all subjects who receive any QR-110 with at least one baseline and one post baseline efficacy observation or measurement.

Per Protocol Efficacy Population: this population will consist of all eyes in the Efficacy Evaluable Population with the exception of eyes with major protocol deviations who will be excluded. The list of major protocol deviations for exclusion from this population will be completed prior to database lock.

Pharmacokinetics Population: the population for PK analyses will consist of all subjects who receive QR-110 and who have measurable drug concentrations in blood samples.

10.4 Subject Disposition, Demographics and Baseline Disease Characteristics

Subject disposition will be summarized for the safety population by dose group and age. The number and percentage of subjects enrolled in each study center will be presented by geographic region (North America and Europe).

The number and percentage of subjects who receive QR-110 will be tabulated by the number of doses and the QR-110 dose group.

Subject demographics and baseline characteristics will be summarized for each dose group, age, and for all subjects combined. Subject characteristics at baseline include age, race, body weight, and height. Baseline disease characteristics include ophthalmic examinations, measurements and tests, as previously described. Baseline data is defined as the data most recently collected and/or the measure reflecting the highest level of visual function (eg, for ophthalmic assessments performed two or more times) prior to the first dose of study drug in this or study PQ-110-001.

10.5 Treatment Compliance

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

10.6 Safety Analyses

10.6.1 Treatment Emergent Adverse Events

A treatment emergent adverse event (TEAE) is defined as an event that was not present prior to administration of the first dose of study drug and present after the first dose or if it represents the exacerbation of an event that was present prior to the first 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 summarized by dose group and classified by SOC and PT. Deaths, AE severity, seriousness, relationship to study drug and study discontinuation due to AE will also be tabulated by dose group. An AE will be considered drug-related if the Investigator indicated the event is at least "possibly" related or if the relationship is missing. Adverse events with missing start dates, but with stop dates overlapping into the treatment period will be counted as treatment emergent. All AEs will be listed in subject listing and summarized by numbers and percentages of subjects by dose for each portion of the study separately. If a subject reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the treatment-related events will be included in the summary tables of TEAEs.

10.6.2 Vital Signs

Vital signs measurements will consist of heart rate, blood pressure and temperature. Descriptive summaries (number of subjects, mean, standard deviation, median, minimum, and maximum) of actual values and changes from baseline will be presented for each time point. These summaries will be presented for the safety population and by dose group.

10.6.3 Laboratory Assessments

Laboratory measurements (hematology, chemistry and urinalysis) obtained at baseline and each study visit will be summarized by dose group and age by:

- Descriptive statistics of actual results (number of subjects, mean, standard deviation, median, minimum, and maximum) for the continuous data and frequencies and percentages for the categorical data, for each time point.
- Descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) of change from baseline to each time point.
- Shift tables summarizing the frequencies of subjects below, within and above the normal ranges at baseline and at each time point.

10.6.4 Other Safety Assessments

Other safety assessments, such as ophthalmic exams, OCT, infrared imaging, ECGs and physical examinations will be summarized and listed as specified in the SAP.

10.7 Pharmacokinetics Analyses

To determine the PK profile of IVT injections at the different dose levels of QR-110, the following PK parameters will be calculated if sufficient data are available for each dose:

- $AUC_{0-\infty}$: Area under the curve to infinity will be calculated based on the last observed concentration (C_{last} [obs]) using formula: $AUC_{0-\infty}=AUC_{last}+C_{last}(obs)/elimination\ rate\ constant\ (\lambda_z)$, if feasible.
- $AUC_{0-tlast}$: Area under the curve to the final sample with a concentration greater than lower limit of quantification (LLOQ) will be calculated based on the last observed concentration using the linear trapezoidal method.
- C_{max}, C_0: The maximum and minimum serum concentrations will be taken directly from the data.
- T_{max}: Time to C_{max} will be taken directly from the data.
- $T_{1/2}$ (if measurable serum levels are obtained): The terminal elimination half-life will be estimated by non-linear regression analysis of the terminal elimination slope, if feasible.
- CL: Serum clearance will be estimated using the formula: $CL = Dose/AUC_{0-\infty}$.
- V_d (if measurable serum levels are obtained and a λ_z is estimable): Apparent volume of distribution at steady state of the drug will be determined from trough levels.

Serum concentration below lower limit of quantification (LLOQ) prior to dose for the assay will be set to zero for the PK analysis. For other cases concentrations below LLOQ will be set for non-informative missing. Exact procedure for imputation of data will be described in the SAP.

All samples obtained from all cohorts will be analyzed to avoid bias in data presentation.

Sparse sampling analysis may be used to mitigate the risk of insufficient data to create individual profiles.

Drug concentrations will be summarized by nominal time point if 3 or more values are available. Descriptive statistics for PK parameters will be performed if ≥ 50% of subjects have evaluable data and number of values to summarize is ≥ 3.

Geometric means and coefficients of variation will be tabulated for C_{max}, C_0, $AUC_{0-tlast}$, $AUC_{0-\infty}$, CL, and V_d for each dose group if possible. T_{max} will be summarized by median, minimum and maximum. Mean, standard deviation, minimum and maximum will be provided for $T_{1/2}$. Exact details for statistical analysis of PK concentrations and derived PK parameters will be presented in the Pharmacokinetic Analysis Plan.

10.8 Efficacy Analyses

The secondary efficacy evaluations will include changes from baseline in:

- BCVA
- Mobility course score
- FST

- OCI
- OCT (Change in photoreceptor outer segment layer thickness)
- PLR
- NIRAF
- VFQ-25 (adult subjects)
- CVAQC (pediatric subjects)

Descriptive statistics of clinical efficacy will be tabulated by dose group, age, and genetic status, and if appropriate, for dose groups combined.

All continuous endpoints will be summarized using the following descriptive statistics: number of subjects, mean, standard deviation, standard error, median, minimum, maximum and 95% confidence intervals for the mean. Continuous efficacy endpoints will be summarized and may be analyzed using appropriate parametric or nonparametric inference tests.

Categorical endpoints will be summarized using: number of subjects, frequency, percentages and 95% confidence intervals. If data appear highly skewed, natural log or other transformation may be used to compute summary statistics.

Details of the statistical analyses can be reviewed in the SAP.

10.9 Exploratory Analyses

10.10 Interim Analysis

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

10.11 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 and Study Monitoring

An eCRF will be used for this study. Study center personnel will be trained and authorized to use the system in compliance with the Code of Federal Regulations (CFR) 21CFR Part 11, International Council on Harmonization 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. All subjects screened for the study who sign an Informed Consent Form or assent document will be assigned a subject screening number that will be entered in the Screening and Enrollment Log. The subject screening number will be a unique 4-digit subject identifier: a 2-digit site number and a consecutive 2-digit subject screening number. 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 screen fail. At the study's conclusion, a Portable Document Format file will be created for each study center containing their subjects' data submitted on eCRFs. In the event of an audit or regulatory authority inspection, copies of the eCRFs will be printed. 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.

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.

The Investigator will electronically sign and date the indicated places on the eCRF. These signatures will indicate that the Investigator inspected or reviewed the data on the eCRF and agrees with the content.

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. No other personal information will be disclosed to the monitor.

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.

11.2 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 systematically and independently examine all study-related activities and documents, 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 participant (or the subject's legal representative) in accordance with ICH GCP, and country authority requirements. Age appropriate assent and permission from a minor subject's parent or legal guardian is required for pediatric subjects. The subject or his/her legal representative must sign the current version of the written, IRB/EC-approved Informed Consent Form 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.

Subjects may be asked to sign separate Informed Consent Forms for gene sequencing, lens tissue and aqueous humor collection, and travel assistance. Consent for travel assistance may also be obtained prior to the Screening Visit. Consent for gene sequencing and/or lens tissue and aqueous humor collection may be obtained at any time during the study.

In accordance with ICH GCP and country authority requirements, an IRB/EC must review and approve this protocol and the Informed Consent Form 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 Informed Consent Form, assent forms, parental permission 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 Informed Consent Form 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 Informed Consent Form, 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 must ensure that the subject's confidentiality is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should be identified by their date of birth (month and year) and subject number only. Documents that are not for submission to the Sponsor (eg, signed Informed Consent Forms), should be kept in strict confidence by the Investigator.

In compliance with applicable regulations, it is required that the Investigator and institution permit authorized representatives of the Sponsor, the US FDA, other regulatory authorities, 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.

13.0 STUDY ADMINISTRATION

13.1 Investigator's Brochure

Before the study begins, the Investigator will receive the QR-110 IB describing all known 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, then these changes will be documented in a protocol amendment and in a new version of the protocol. Protocol amendments must be made only with the prior approval of the Sponsor. The Sponsor will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any Informed Consent Form 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.

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, 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 or administrative reasons.

If the clinical development of QR-110 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 (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 informed consents 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 subject dairies and 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 information 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 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.

13.6 End of Study and Final Report

In North America, the Investigator or associate must notify the IRB/EC when the study is closed. If not initially provided by the Sponsor, a copy of the final study report must also be provided to Sponsor or its representative.

In the European Union, the Sponsor or its designee must notify the Competent Authorities and ECs within 90 days of completion of the study in the concerned country and/or worldwide in accordance with local requirements. In case of early termination, the deadline is 15 days. The Sponsor or its designee must provide a final report and/or synopsis to the European Competent Authorities and ECs at the latest 1 year after the study termination worldwide, in accordance with local requirements. A copy of this final report and associated synopsis must also be provided to the Investigator.

End of Study will be defined as the last study visit for the last subject.

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.

14.0 REFERENCES

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15.0 APPENDICES

APPENDIX 2: CLINICAL LABORATORY ANALYTES

Serum Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Calcium
Chloride	Creatinine
Creatinine clearance (eGFR) [1]	Gamma-glutamyl transferase
Glucose	INR
Potassium	Lactic dehydrogenase
Sodium	Phosphorus
Total and direct bilirubin	Total protein
Uremia or blood urea nitrogen	Uric acid

1. Estimated glomerular filtration rate by CKD-EPI for adults and eGFR by Schwartz for pediatrics (Section 8.3).

Hematology

A complete blood count will include:

Hematocrit	Hemoglobin
Red blood cell count	White blood cell count and differential [1]
Neutrophils	Granulocytes
Lymphocytes	Platelets
Eosinophils	Basophils
Monocytes	

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test is acceptable at any visit that warrants a pregnancy test.