CLINICAL STUDY PROTOCOL

AN OPEN-LABEL, MULTIPLE DOSE, DOSE ESCALATION STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF QR-110 IN SUBJECTS WITH LEBER'S CONGENITAL AMAUROSIS (LCA) DUE TO c.2991+1655A>G MUTATION (p.Cys998X) IN THE *CEP290* GENE

Protocol No.	PQ-110-001
Protocol/Amendment Date:	02-Aug-2018
Protocol/Amendment No.:	05
Protocol Version:	6.0
Supersedes:	Protocol version 3.0, 4.0 and 5.0
EudraCT/IND Number	2017-000813-22/130557
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
CRO Medical Monitor	
Sponsor Medical Monitor: **Telephone Number:**	

INVESTIGATOR SIGNATURE PAGE

PRINCIPAL INVESTIGATOR COMMITMENT:

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

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

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

_____

Institution

_____

Address of Institution

_____

Phone Number of Investigator

PROTOCOL APPROVAL PAGE

An Open-Label, Multiple Dose, Dose Escalation Study to Evaluate the Safety and Tolerability of QR-110 in Subjects with Leber's Congenital Amaurosis (LCA) due to c.2991+1655A>G Mutation (p.Cys998X) in the *CEP290* Gene

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SPONSOR: **ProQR Therapeutics**
Zernikedreef 9
2333 CK Leiden
The Netherlands

_____ _____
Date

_____ _____
Date

NATIONAL COORDINATING INVESTIGATORS

Name **Institution** **Street Address** **City, Country, Postal Code**	
Name **Institution** **Street Address** **City, Country, Postal Code**	

1.0 SYNOPSIS

Name of the Sponsor: ProQR Therapeutics **Name of Study Drug:** QR-110 Solution for Intravitreal Injection **Name of Active Ingredient:** QR-110	**Individual Study Table Referring to Part of the Dossier:** **Volume:** NA **Page:** NA	**For National Authority Use Only**
Title of Study:	An Open-Label, Multiple Dose, Dose Escalation Study to Evaluate the Safety and Tolerability of QR-110 in Subjects with Leber's Congenital Amaurosis (LCA) due to c.2991+1655A>G Mutation (p.Cys998X) in the *CEP290* Gene	
Study Centers:	Participation of approximately 3 study centers planned	
Phase of Development:	Phase 1b/2	
Study Period:	Anticipated to be approximately 18 months	
Duration of Subject Participation:	13 months (Screening 28 days; study period 12 months)	
Rationale:	Leber's 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). 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. QR-110 is a single stranded, chemically modified, RNA oligonucleotide that is designed to correct aberrant splicing in *CEP290* gene, enabling production of fully functional RNA and protein.	
Objectives:	Primary: To evaluate the safety and tolerability of QR-110 administered via intravitreal (IVT) injection in subjects with LCA due to the *CEP290* p.Cys998X mutation Secondary: To evaluate the serum pharmacokinetics of QR-110 administered by IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation To evaluate the efficacy of QR-110 administered by IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation	
Number of Subjects (planned):	12 The final number of subjects is dependent on whether any dose levels are expanded by the Data Monitoring Committee (DMC) and Sponsor Medical Monitor.	
Study Design	The first-in-human study of QR-110 will be an open-label, multiple dose, dose escalation study to evaluate the safety and tolerability of QR-110 administered via IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation. Subjects will	

	be assigned to receive a specified dose level of QR-110 (loading dose and maintenance dose) and will receive that dose throughout their participation, while they are monitored for safety. No intrasubject dose escalation is planned. Up to 3 dose levels of QR-110 will be evaluated. Dose escalation decisions and initiation of dosing in pediatric subjects (6 to <18 years of age) will be determined by the DMC and Sponsor Medical Monitor review of safety and tolerability data. The DMC and Sponsor Medical Monitor will also review all available safety data at key study time points (eg, prior to the first subject in the first adult cohort (Cohort A1) receiving each subsequent dose of study drug). QR-110 will be administered by unilateral IVT injection. Each subject will receive up to 4 doses of QR-110 in their worse eye (as defined by visual acuity at Screening, subsequently referred to as treatment eye) every 3 months and will be assessed for safety and tolerability at follow up visits. If both eyes have the same visual acuity, the Investigator should determine the eye with the worse visual function as the treatment eye, according to other measures of ophthalmic function (Full-field Stimulus Testing [FST] or mobility course score). If the visual function is the same per the Investigator's assessment, then the treatment eye will be determined at Investigator discretion. No placebo nor sham injections will be administered in the contralateral eye. The contralateral eye and the subject's own baseline measurements will serve as controls. Subjects who do not meet stopping criteria prior to their next scheduled injection will receive their planned dose (Section 4.2.2). Subjects who meet stopping criteria will be discontinued from dosing and will be followed for safety and efficacy. The DMC and/or Sponsor Medical Monitor may decide to de-escalate the dose, hold the dose (delay or skip), or discontinue study drug for an individual subject, in consultation with the Investigator. Subjects who discontinue study drug will continue to be followed for safety and efficacy. An extension study, which would permit continued dosing of eligible subjects who complete PQ-110-001, is planned. **Dose Escalation** Specifics of the dose escalation plan are described in detail in Section 4.2.1.5. It is planned to dose at least 2 adults and, subsequently, at least 2 pediatric subjects at each dose level of QR-110. Up to 3 dose levels are planned across 3 dose cohorts. No intrasubject dose escalation will occur. Dosing will be staggered such that: • The first 2 subjects at any dose level will be dosed at least 2 weeks apart • At least 4 weeks of post dose safety and tolerability data on the previous cohort will be reviewed by the DMC and Sponsor Medical Monitor prior to dose escalation in subsequent subjects • Dosing and dose escalation of pediatric cohorts will be initiated following DMC and Sponsor Medical Monitor review and will follow that of the corresponding adult cohort by at least 4 weeks Following DMC and Sponsor Medical Monitor review and decision on dose escalation, the first subject at the next dose level may be dosed and the second subject at that dose level may be dosed 2 weeks later. Safety and tolerability data, including follow-up for at least 4 weeks post dose, will be reviewed by the DMC and Sponsor Medical Monitor. A complete discussion of the rules regarding timing of doses for individual subjects is presented in Section 4.2.1.5. Pediatric subjects will only receive a given dose level of QR-110 following DMC and Sponsor Medical Monitor acceptance of at least 4 weeks of post dose safety and

	tolerability data in the 2 adults at that same dose level. Therefore, dosing of pediatric subjects will remain a minimum of 4 weeks behind dosing of the corresponding adult cohort at the same dose level. The safety measures around the timing of dosing and dose escalation of adult subjects also apply to pediatric subjects. The first 2 pediatric subjects at each dose level will be dosed at least 2 weeks apart. At least 4 weeks of safety and tolerability data for the first 2 pediatric subjects at each dose level will be reviewed by the DMC and Sponsor Medical Monitor prior to enrollment and dose escalation of subsequent pediatric subjects. Safety review will be conducted by the DMC and Sponsor Medical Monitor before each cohort initiation and on an ad hoc basis as needed. The Sponsor will also perform safety review on an ongoing basis. **Study Plan** The study includes a 28-day screening period. During the screening period, subjects will be assessed according to the eligibility criteria. Historic genotyping results from a certified genetic laboratory are acceptable with Sponsor approval. For subjects without a historic genotyping result, genotyping and gene sequencing analysis to determine the presence of the *CEP290* p.Cys998X mutation will be performed. It is recommended that screening be conducted in a stepwise manner, so that eligibility is confirmed first with less intensive assessments and more intensive assessments are conducted after eligibility by all other criteria have been confirmed. Most measures of visual function (Best-corrected Visual Acuity [BCVA], FST mobility course, oculomotor instability and Pupillary Light Reflex [PLR]) will be measured a minimum of 2 times prior to the subject's first dose of study drug to evaluate intrasubject variability (Screening and predose on Day 1). Measures of retinal anatomy (infrared imaging, and Optical Coherence Tomography [OCT]) and electroretinogram (ERG) will be measured a minimum of 1 time prior to the subject's first dose of study drug. Any predose 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. In the case of repeat assessments, the measure reflecting the average of the measures will be considered the Baseline value. Subjects who meet all eligibility criteria will be enrolled into the study and will receive their first dose of study drug on Day 1. QR-110 will be administered via IVT injection into the subject's treatment eye in accordance with the procedures outlined by the American Academy of Ophthalmology (Avery 2014). Subjects will be monitored clinically for increases in intraocular pressure (IOP) and signs of inflammation and endophthalmitis during the post-injection period. Subjects will be evaluated the day after each administration of study drug for safety monitoring (all doses) and to enable collection of serum samples for pharmacokinetic (PK) analysis Subjects will return to the study center to complete safety assessments at 7 days, and 1 month, 2 months (doses 1 and 2 only) and 3 months post dose. In addition, subjects will be evaluated by telephone interview at 14 days post dose for the first dose only. Efficacy assessments, including retinal imaging, functional assessments of vision, All assessments will be performed on both the treatment and contralateral eyes.

	The Investigator, Sponsor Medical Monitor and/or the DMC may decide to stop treatment for an individual subject due to an adverse event (AE). Stopping criteria are described in Section 4.2.2.
Diagnosis and Main Criteria for Eligibility:	Inclusion Criteria: 1. Male or female, ≥ 6 years of age at Screening with a clinical diagnosis of LCA and a molecular diagnosis of homozygosity or compound heterozygosity for the *CEP290* p.Cys998X mutation, based on genotyping analysis at Screening. Historic genotyping results from a certified laboratory are acceptable with Sponsor approval. 2. Best-corrected visual acuity greater than or equal to light perception in both eyes and equal to or worse than Logarithm of the Minimum Angle of Resolution (LogMAR) + 0.6 (Snellen notation 20/80) in the worse eye and equal to or worse than LogMAR + 0.4 (Snellen notation 20/50) in the contralateral eye. 3. Detectable outer nuclear layer (ONL) in the area of the macula in the opinion of the Investigator, as determined by OCT 4. An ERG result consistent with LCA, as determined by the Investigator and the Reading Center. A historic ERG result is acceptable for eligibility. 5. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator 6. 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 7. 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 8. Female subjects of childbearing potential, who have reached menarche, and male subjects must be sexually inactive by abstinence, which is consistent with the preferred and usual lifestyle of the subject, or agree to use adequate birth control, as defined in Section 6.2.3. Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in Section 6.2.3. 9. Adequate verbal communication as to allow assessment via mobility course, in the opinion of the Investigator No waivers to the inclusion criteria are permitted. Exclusion Criteria: 1. Diagnosed with an inherited retinal degenerative disease other than LCA or diagnosed with LCA due to a mutation in *CEP290* which does not include at least one copy of p.Cys998X, either in homozygosity or compound heterozygosity. Note: The confirmed presence of known disease causing mutations in other genes involved in retinal dystrophy is exclusionary. 2. Syndromic disease such as Alström syndrome, Batten disease, Joubert syndrome, peroxisomal diseases and Senior-Løken syndrome or other disease with similar presentation

	3. Any contraindication to IVT injection according to the Investigator's clinical judgment and international guidelines (Avery 2014) 4. Pregnant or breast-feeding female 5. Any clinically significant cardiac disease or defect, in the opinion of the Investigator 6. Personal or family history of prolonged QT syndrome or QTcF ≥ 450 ms (adult subjects and pediatric subjects >10 years old) or QTcB ≥ 450 ms (pediatric subjects ≤10 years old) by electrocardiogram (ECG) at Screening NOTE: Exclusion criteria 7 through 9 are related to acceptable laboratory values at Screening. Subjects with a screening laboratory value outside of the specified range may be permitted if the value is not clinically significant in the opinion of the Investigator, with concurrence from the Sponsor's Medical Monitor. 7. Estimated Glomerular Filtration Rate (eGFR) less than the lower limit of normal 8. Aspartase Aminotransferase (AST) or Alanine Aminotransferase (ALT) greater than 1.2x the upper limit of normal 9. One or more coagulation parameters (platelet count, International Normalized Ratio [INR]) outside of the normal range 10. Any ocular disease or condition that could compromise treatment safety, visual acuity or interfere with assessment of efficacy and safety, as determined by the Investigator 11. Prior receipt of intraocular surgery or IVT injection within 3 months prior to study start or planned intraocular surgery or procedure during the course of the study 12. Use of any investigational drug or device within 90 days or 5 half-lives of Day 1, whichever is longer, or plans to participate in another study of a drug or device during the PQ-110-001 study period 13. Any prior receipt of genetic therapy for LCA 14. Any severe, acute or chronic medical or psychiatric condition, including substance abuse, laboratory abnormality or other condition that, in the judgment of the Investigator, would place the subject at undue risk, interfere with the results of the study, or make the subject otherwise unsuitable 15. History of malignancy within 5 years prior to Screening, except adequately treated cutaneous squamous or basal cell carcinoma No waivers to the exclusion criteria are permitted.

Endpoints:	**Primary** • Frequency and severity of ocular AEs in the treatment and contralateral eyes **Secondary** • Frequency and severity of non-ocular AEs • Changes in ophthalmic examination findings • Change in BCVA • Changes in infrared imaging • Changes in OCT findings • Changes in safety parameters, including vital sign measurements, physical examination findings, ECG and laboratory parameters • Characterize the PK profile of QR-110 in serum • Change in light sensitivity to red FST • Change in light sensitivity to blue FST • Change in amplitude to white PLR • Change in latency to white PLR **Exploratory**
Study Drug, Dosage and Mode of Administration:	QR-110 Solution for IVT Injection, Up to 3 dose levels will be tested (loading dose/maintenance dose): 160 µg/80 µg, 320 µg/160 µg, and 500 µg/270 µg. QR-110 will be administered every 3 months for a total of 4 doses per subject.
Duration of Treatment:	12 months
Reference Therapy, Dosage and Mode of Administration:	Not applicable

Criteria for Evaluation:	
Safety and Tolerability:	• Frequency and severity of ocular and non-ocular AEs • Ophthalmic examination findings • BCVA • Infrared imaging • OCT • Vital sign measurements • Physical examination findings • ECG • Laboratory parameters
PK:	• Subjects will provide blood samples for presence of QR-110 at multiple time points
Efficacy:	• BCVA • White PLR • Red FST • Blue FST

Statistical Methods:	Baseline demographics and disease characteristics, safety and efficacy endpoints will be summarized descriptively by dose group and for all subjects combined. Continuous efficacy endpoints will be summarized and may be analyzed using appropriate parametric or nonparametric inference tests. Serum concentrations of QR-110 will be summarized by dose level and time point. 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: $AUC_{0-\infty}=AUC_{last}+C_{last}(obs)/\lambda z$, 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 an elimination rate constant (λ_z) is estimable): Apparent volume of distribution at steady state of the drug will be determined from trough levels. Any p values that will be calculated according to the analysis plan will be interpreted in view of the exploratory nature of the study. Details on statistical analyses will be included in the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
A	Adenine
AE	Adverse Event
ALT	Alanine Aminotransferase
AON	Antisense Oligonucleotide
AREDS	Age-Related Eye Diseases Study
ARLNS	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
BUN	Blood Urea Nitrogen
C	Cytosine
CBC	Complete Blood Count
CEP290	Centrosomal Protein 290 kDa
CEP290	CEP290 gene
CF	Counting Fingers
CFR	Code of Federal Regulations
CH50	C4, Hemolytic complement 50
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
CRP	C Reactive Protein
C_{max}	Maximum Concentration
C_0	Trough Value
CSR	Clinical Study Report

DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
ERG	Electroretinogram
ESE	Exonic Splicing Enhancer
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FST	Full-field Stimulus Testing (also, Full-field Stimulus Threshold Testing or Full-field Scotopic Threshold Testing)
G	Guanine
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
HM	Hand Motion
IB	Investigator's Brochure
ICH	The International Council on Harmonisation
INR	International Normalized Ratio
IOP	Intraocular Pressure
iPSC	Induced Pluripotent Stem Cells
IRB	Institutional Review Board
IVT	Intravitreal
LCA	Leber's 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
NIH	National Institute of Health
OCI	Oculomotor Instability
OCT	Optical Coherence Tomography
ONL	Outer Nuclear Layer
PBS	Phosphate Buffered Saline
p.Cys998X	c.2991+1655A>G mutation in the *CEP290* gene
PD	Pharmacodynamic
PK	Pharmacokinetic
PLR	Pupillary Light Reflex
ProQR	ProQR Therapeutics
PT	Preferred Term
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
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
T_{min}	Time of minimum concentration
ULN	Upper Limit of Normal
US	United States
V_d	Volume of Distribution
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's 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's 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). 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's Congenital Amaurosis

Leber's 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's Congenital Amaurosis due to *CEP290* p.Cys998X Mutation

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 p.Cys998X mutation.

QR-110 is an AON designed as a disease modifying therapy for LCA due to the *CEP290* p.Cys998X mutation. QR-110 targets the splicing mutation of the CEP290 protein through a mechanism of RNA modulation that skips the inclusion of the cryptic exon-X. The exclusion of this cryptic exon results in restoration of the open reading frame of *CEP290* and excludes the premature stop codon present in exon-X.

2.2.2 Clinical Experience

No clinical studies have been conducted with QR-110 Solution for IVT Injection.

2.3 Study Rationale

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. QR-110 is designed to target the splicing mutation in the CEP290 protein. The hybridization of the QR-110 oligonucleotide modulates the RNA splicing process, blocking access to the active cryptic splice site and restoring preference for the wild-type splice sites, skipping the inclusion of the cryptic exon-X in *CEP290*, and resulting in a functional CEP290 protein.

This first-in-human study of QR-110 is an open-label, multiple dose, dose escalation study to evaluate the safety and tolerability of QR-110 administered via IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation. It is anticipated that repair of the splicing defect may be possible in patients with preservation of at least detectable ONL. Patients with LCA due to the *CEP290* p.Cys998X mutation exhibit progressive retinal degeneration and substantial loss of rod photoreceptors in the peripheral retina; however, sparing of foveal/macular cone photoreceptors has been observed. Such cone photoreceptor sparing is noted in some patients by the presence of an almost normal retinal ONL thickness at the foveal region and retained cone-specific retinal function. Importantly, age does not seem to be strictly associated with disease severity (Cideciyan 2007, Cideciyan 2011, Pasadhika 2010).

The phenotype of LCA due to mutations in *CEP290* is severe. However, in a cohort of Dutch patients, Yzer et al (2012) concluded that patients usually have a relatively normal optic disc, mild or moderate attenuation of vessels and a relatively preserved posterior pole, suggesting that anatomy is preserved. There is evidence of sparing of some photoreceptors in the macula of individuals with LCA carrying *CEP290* mutations, which may allow for therapeutic intervention.

Restoration of protein expression to wild-type levels has the potential to delay, cease, or possibly to reverse disease progression (Chacon-Camacho 2015).

2.3.1 Rationale for Open-label Design in Patients

Intravitreal injection is a well-established route of administration within ophthalmic indications; however, rare but potentially serious complications to IVT injections exist, including acute onset endophthalmitis, pseudo-endophthalmitis, cataract and retinal detachment. Although the risk of serious complications is small, it is well-documented (Artunay 2009, Fagan 2013, Falavarjani 2013). Therefore, placebo injections will not be administered in this study to preserve subject safety.

Use of sham injections to mask subjects to treatment assignment in studies of products administered via IVT injection eliminates the risk of complications due to injection in the contralateral eye. Sham injections that closely mimic the active injection can effectively mask participants to treatment assignment; however, the masking effect is less pronounced in the case where a single subject would receive both the real and sham injections, one in each of their eyes (Glassman 2012), as would be required in LCA due to the *CEP290* p.Cys998X mutation.

This study will be an open-label study and sham injections will not be used. Masking of participating subjects is of particular importance when subject effort or perception could bias evaluation of study endpoints; this is true for the assessment of subjective endpoints such as visual acuity (Glassman 2012). However, many assessments are objective tests (Pupillary Light Reflex [PLR], OCT, oculomotor instability [OCI], ERG, and infrared imaging) which are not related to subject responses. A central reading center will be used for several of the ophthalmologic assessments, including PLR, OCI, Full Field Stimulus Testing (FST), ERG, OCT and infrared imaging, which will be reviewed and interpreted by an independent masked evaluator. Mobility course scoring will also be reviewed and calculated by a masked evaluator. Furthermore, this study will evaluate safety and tolerability as the primary endpoint. Measures of safety will be monitored and severity and causality determined by the Investigator. Taken together, the risk of the introduction of bias to the determination of safety from the participant is low and sham injections will not reduce bias introduced by Investigators.

Subjects will receive QR-110 as a unilateral IVT injection in their worse eye (see Section 4.2.1.2). Treatment of the worse eye is common practice in the development of ophthalmic products (Bainbridge 2008, Ghazi 2016, Jacobson 2012, Maguire 2009). Unilateral injection serves as an additional means to ensure safety, as visual function is driven by a subject´s better eye. Unless otherwise specified, both safety and efficacy evaluations -will be based on the assessment of the treatment eye in comparison to baseline measures and to the untreated eye (referred to hereafter as the contralateral eye). As there is no approved therapy for the treatment of LCA due to the *CEP290* p.Cys998X mutation, no suitable comparator currently exists. The contralateral eye, therefore, serves as a control and removes the biases due to the absence of a relevant comparator, or the

administration of placebo by IVT injection, which is considered unethical in this population. Assessments based on both the comparison of the treatment eye to the contralateral eye, and changes from baseline in the treatment eye will provide the strongest comparisons from which to evaluate safety and efficacy data.

2.4 Route of Administration, Dosage, Dosage Regimen and Treatment Period

Intravitreal injection is a well-established route of administration within ophthalmic indications. Systemic exposure to drugs administered via IVT injection is generally low and the technique enables targeting of the product to the intraocular tissues of the eye (AAO 2015). Intravitreal injection is used in several products for the chronic treatment of ophthalmic diseases (eg, Lucentis®, Eylea™, Macugen®) and the risk of complications is low when injections are performed by trained ophthalmologists (AAO 2015).

Since IVT injections themselves carry a low risk of serious complications, independent of the product administered, dose levels to be investigated in the study are calculated to be pharmacologically efficacious doses. Evaluation of up to 3 dose levels of QR-110 is planned. Inclusion of up to 3 dose levels enables investigation of a potential dose response relationship for QR-110. Based on the chemistry of the molecule, PK data from toxicology studies, and what is known of other oligonucleotides approved for IVT injection (Macugen®, Vitravene®), systemic absorption is anticipated to be low.

Each subject will receive up to 4 doses of QR-110 at 3 month intervals and will be monitored for 3 months following their last dose of study drug. The dosing interval of 3 months and the 12-month duration of dosing is expected to be in the efficacious range for QR-110. Administration of 4 doses has been selected to enable evaluation of the safety of repeat dosing of QR-110 and to evaluate potential efficacy parameters. The multiple dose design provides subjects with the potential opportunity for efficacy. A single dose design is not considered acceptable in this population because subjects would be exposed to the risks associated with IVT injection without the possibility of being able to derive any (sustained) benefit. To ensure subject safety in this multiple dose design, an independent Data Monitoring Committee (DMC) will review all available safety data prior to each dose escalation, prior to inclusion of pediatric subjects, and prior to the first subject receiving each subsequent dose of QR-110 (doses 2, 3, and 4). Therefore, the study consists of a single initial dose, with DMC review of cumulative study data and a positive DMC recommendation prior to continuing to each subsequent dose.

2.4.1 Dose Selection Rationale

The proposed starting dose and escalation scheme for PQ-110-001 is considered conservative.

The proposed dosing regimens to be studied are as follows:

- Low dose: 160 µg loading dose, followed by up to three 80 µg maintenance doses
- Middle dose: 320 µg loading dose, followed by up to three 160 µg maintenance doses
- High dose: 500 µg loading dose, followed by up to three 270 µg maintenance doses

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

2.5 Study Population

The study drug will be administered by IVT injection which carries a risk of serious complications, making the inclusion of healthy volunteers unethical. Furthermore, QR-110 is designed to exert the specific effect of masking the cryptic splice site in patients with the *CEP290* p.Cys998X mutation, which is not present in healthy volunteers. It is, therefore, unknown if safety data obtained from healthy volunteers, would be similar to that of patients with the target mutation. Evaluation of patients with LCA due to the *CEP290* p.Cys998X mutation is therefore necessary to evaluate the safety of QR-110.

Eligible subjects will have LCA due to homozygosity or compound heterozygosity for the *CEP290* p.Cys998X mutation, residual vision and detectable ONL in the area of the macula as determined by OCT. Preservation of at least some retained photoreceptor ONL is a prerequisite for restoration of the splicing defect and consequent impact on disease. Due to severe nystagmus in many subjects with LCA due to the *CEP290* p.Cys998X mutation, it is anticipated that consistent, quantitative calculation of the volume of retained ONL across subjects may be a challenge in this population; therefore, eligibility will be determined by the existence of any detectable ONL on OCT, in the opinion of the Investigator.

Since disease severity does not seem to clearly correlate with age, inclusion of subjects in the first-in-human trial should be guided by disease status and potential for obtaining a therapeutic benefit. The high unmet medical need warrants early therapeutic intervention in those patients with sufficient preserved vision and retinal anatomy in which a major clinical benefit (restoration or improvement of vision or delay in visual loss) could potentially be expected. Therefore, treatment with QR-110 is justified in those patients with LCA due to the *CEP290* p.Cys998X mutation who present detectable ONL, irrespective of age.

2.5.1 Inclusion of Pediatric Subjects

Symptoms of LCA due to the *CEP290* p.Cys998X mutation occur in young pediatric patients; symptoms are usually detected before 1 year of age and patients show severe vision disturbances. Pediatric patients could benefit from treatment with a therapy for LCA due to the *CEP290* p.Cys998X mutation beginning at a very young age. Given the timing of symptom onset and substantial vision loss in young children, it is possible that early initiation of treatment may result in improved clinical outcomes for patients. While the potential to at least cease progression can

be assumed to be most beneficial to younger patients, the target patient population for the first-in-human study of QR-110 will only include pediatric patients at least 6 years of age to ensure subject safety and due to the complexity of study assessments. A staggered approach has been selected such that pediatric subjects (pediatric patients include those 6 to less than 18 years of age) will only start treatment following review of safety and tolerability data from adult subjects (adult subjects include those ≥18 years of age).

In pediatric subjects at least 6 years of age, the average volume of vitreous is similar to that of adult subjects, as referred in Bhardwaj et al (2013) and Zadnik et al (2004). Intravitreal administration of anti-Vascular Endothelial Growth Factor A agents is used to treat newborns in cases of Retinopathy of Prematurity and no issues specific to the pediatric population have been identified in connection to the IVT injection (Mintz-Hittner 2008, Nazari 2010). For a product given via IVT injection, there is no evidence to suggest that the safety profile would differ in adult patients as compared to pediatric patients at least 6 years of age. Toxicity studies in juvenile animals are summarized in the QR-110 IB, Nonclinical Studies.

For the purposes of an early phase clinical study such as PQ-110-001, it is essential that participating subjects be able to complete all necessary safety and efficacy assessments; therefore, specifying a minimum age for subject eligibility is appropriate. The psychophysical tests used in low vision populations are difficult for children younger than 6 years of age to complete due to complexity and the level of focus required. In practice, the ability to complete these tests, based on the individual child and the suitability of patients of any age to complete all required assessments, will be determined by the Investigator. Furthermore, the visit frequency for this first-in-human trial will be high and visit duration lengthy due to the large number of measures required to assess safety. Therefore, the target patient population for the PQ-110-001 study will be patients at least 6 years of age who are able to complete all study assessments, in the opinion of the Investigator.

2.5.2 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).

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of QR-110 administered via IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation.

3.2 Secondary Objectives

The secondary objectives of the study are:

- to evaluate the serum pharmacokinetics of QR-110 administered by IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation
- to evaluate the efficacy of QR-110 administered by IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation

3.3 Exploratory Objective

4.0 STUDY OVERVIEW

4.1 Criteria for Evaluation

4.1.1 Primary Endpoint

- Frequency and severity of ocular AEs in the treatment and contralateral eyes

4.1.2 Secondary Endpoints

- Frequency and severity of non-ocular AEs
- Changes in ophthalmic examination findings
- Change in BCVA
- Changes in infrared imaging
- Changes in OCT findings
- Changes in safety parameters, including vital sign measurements, physical examination findings, electrocardiogram (ECG) and laboratory parameters

- Characterize the PK profile of QR-110 in serum
- Change in light sensitivity to red FST
- Change in light sensitivity to blue FST
- Change in amplitude to white PLR
- Change in latency to white PLR

4.1.3 Exploratory Endpoints

The study is not designed to have sufficient statistical power to assess efficacy of QR-110 in the treatment of LCA due to the *CEP290* p.Cys998X mutation. However, changes in clinical outcome measures associated with LCA due to the *CEP290* p.Cys998X mutation will be monitored over the course of the study.

4.2 Study Design

The first-in-human study of QR-110 will be an open-label, multiple dose, dose escalation study to evaluate the safety and tolerability of QR-110 administered via IVT injection in subjects with LCA due to the *CEP290* p.Cys998X mutation. Subjects will be assigned to receive a specified dose level (loading dose and maintenance dose) of QR-110. No intrasubject dose escalation is planned. Up to 3 dose levels of QR-110 will be evaluated. Dose escalation decisions and initiation of dosing in pediatric subjects will be determined by the DMC and Sponsor Medical Monitor review of safety and tolerability data.

4.2.1 Study Plan

4.2.1.1 Screening

During the screening period, subjects will be assessed according to the eligibility criteria.

Subjects who meet all eligibility criteria will be enrolled into the study. On Day 1, subjects will undergo a second set of predose baseline measures as specified in the SOE and will subsequently receive their first dose of study drug. The data obtained from these two predose measures will serve to inform the level of intrasubject variability in study assessments (see Section 7.2 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 worse eye as defined by visual acuity (subsequently referred to as treatment eye) and will be assessed for safety and tolerability at follow up visits. If both eyes have the same visual acuity, the Investigator should determine the eye with the worse visual function, according to other measures of ophthalmic function at Screening (FST or mobility course score), as the treatment eye. If the visual function is the same per the Investigator's assessment, then the treatment eye will be determined at Investigator discretion.

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

4.2.1.3 Assessment and Follow-up

To closely monitor subject safety, subjects will be evaluated by the Investigator following each IVT injection and the following day, as well as 7 days, 14 days (first dose only, visit to be done via phone call), 1 month, 2 months (doses 1 and 2 only) and 3 months post dose. These frequent in-clinic visits are designed to ensure any untoward events in study subjects are quickly identified under the oversight of the Investigator and can be treated promptly.

Efficacy assessments will be performed according to the SOE. (See Section 7.3 for details on dosing and follow-up visit procedures.)

All study assessments will be performed for both the treatment and contralateral eyes.

4.2.1.4 Study Cohorts

QR-110 will be administered at up to 3 escalating dose levels. The study will include up to 6 cohorts (up to 3 adult cohorts and up to 3 pediatric cohorts). Each cohort will have at least 2 subjects and each dose level will be tested in 1 adult cohort and 1 pediatric cohort (Table 2). Dose escalation will proceed as described in Section 4.2.1.5. QR-110 will be administered via unilateral IVT injection in the subject's worse eye (Section 4.2.1.2) every 3 months and each subject will receive up to 4 doses of study drug.

Table 2: Dose Cohorts

Dose Level	Adult Cohort (at least 2 Subjects)	Pediatric Cohort (at least 2 Subjects)
Low	Cohort A1	Cohort P1
Mid	Cohort A2	Cohort P2
High	Cohort A3	Cohort P3

Details and instructions to Investigators regarding cohort enrollment and management are provided in the Study Reference Manual.

4.2.1.5 Dose Escalation

The study will test loading and maintenance doses of QR-110 from an initial dose of 160 µg/80 µg (loading dose/maintenance dose) to a maximum dose of 500 µg/270 µg (loading dose/maintenance dose) given by IVT injection every 3 months for a total of 12 months (4 doses). At each dose level, safety and tolerability data for at least 4 weeks post dose for the current cohort will be reviewed by the DMC and Sponsor Medical Monitor.

4.2.2 Stopping Criteria

4.2.2.1 Stopping Criteria for Individual Subjects

The Investigator, the DMC or the Sponsor Medical Monitor may stop treatment for an individual subject due to an AE (see 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 Sponsor Medical Monitor and DMC must be notified of any subject who stops treatment due to an AE.

The DMC and Sponsor Medical Monitor may decide to de-escalate the dose, hold the dose (delay or skip), or discontinue study drug for an individual subject, in consultation with the Investigator.

Subjects who discontinue study drug will be encouraged to remain in the study for observation. Subjects who discontinue study drug, but do not withdraw consent will continue to be followed for safety through the End of Study (EOS) visit at Month 12. These subjects should complete: 1) all study visits until the time of their next scheduled dose, and 2) the remaining of Visits 8 (Month 3), 13 (Month 6), 17 (Month 9) and 21 (Month 12/EOS).

The DMC and the Sponsor Medical Monitor will perform ongoing safety reviews of systemic and ophthalmic safety data and AEs for safety signal.

Subjects who do not meet stopping criteria prior to their next scheduled injection will receive their planned dose of study drug. If in the interim a subject meets stopping criteria as identified by the Investigator, the Investigator will notify the DMC and an ad hoc meeting will be convened.

4.2.2.2 Stopping Criteria for Cohort

The DMC and Sponsor Medical Monitor should evaluate the totality of safety data from all subjects receiving the same dose level of QR-110 and cumulative data of previous cohort(s), to evaluate whether a safety signal may be present.

Dose escalation may be stopped if it is determined that the limits of safety and/or tolerability have been reached. This decision will be made after a discussion between the Sponsor Medical Monitor and the DMC.

In all cases, the decision to proceed to the next dose level will be made jointly by the DMC and Sponsor Medical Monitor, based on a review and consideration of all available safety and tolerability information for the study subjects.

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.

If a subject withdraws from participation in the study, then his/her subject number cannot be reused. Withdrawn subjects may be replaced (see Section 10.2.2).

4.2.4 Discontinuation of the Study

The DMC and Sponsor Medical Monitor will evaluate the safety and tolerability data as described in Section 4.2.2 and Table 3 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.

In the case of overwhelming efficacy as determined by ongoing analysis of efficacy (see Section 10.9), the DMC and Sponsor Medical Monitor may make a recommendation to discontinue the study.

5.0 SELECTION OF STUDY POPULATION

5.1 Study Population

Subjects with a diagnosis of LCA due to the *CEP290* p.Cys998X mutation who meet all eligibility criteria will be eligible for participation in this study.

5.2 Selection of Subjects

Screening of subjects will be performed within 28 days prior to dosing. Medical and ocular history, concomitant medications, physical examination findings and vital signs will be recorded. Subjects will be evaluated against all 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.

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. Male or female, ≥ 6 years of age at Screening with a clinical diagnosis of LCA and a molecular diagnosis of homozygosity or compound heterozygosity for the *CEP290* p.Cys998X mutation, based on genotyping analysis at Screening. Historic genotyping results from a certified laboratory are acceptable with Sponsor approval.
2. Best-corrected visual acuity greater than or equal to light perception in both eyes and equal to or worse than Logarithm of the Minimum Angle of Resolution (LogMAR) + 0.6 (Snellen notation 20/80) in the worse eye and equal to or worse than LogMAR + 0.4 (Snellen notation 20/50) in the contralateral eye
3. Detectable ONL in the area of the macula in the opinion of the Investigator, as determined by OCT
4. An ERG result consistent with LCA, as determined by the Investigator and the Reading Center. A historic ERG result is acceptable for eligibility
5. Clear ocular media and adequate pupillary dilation to permit good quality retinal imaging, as assessed by the Investigator
6. 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
7. An adult willing to comply with the protocol, follow study instructions, and 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, comply with the protocol and attend study visits with the subject as required, in the opinion of the Investigator
8. Female subjects of childbearing potential, who have reached menarche, and male subjects must be sexually inactive by abstinence, which is consistent with the preferred and usual lifestyle of the subject, or agree to use adequate birth control as defined in Section 6.2.3.

Women of non-childbearing potential may be included without the use of adequate birth control, provided they meet the criteria in Section 6.2.3.

9. 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. Diagnosed with an inherited retinal degenerative disease other than LCA or diagnosed with LCA due to a mutation in *CEP290* which does not include at least one copy of p.Cys998X, either in homozygosity or compound heterozygosity. Note: The confirmed presence of known disease causing mutations in other genes involved in retinal dystrophy is exclusionary.
2. Syndromic disease such as Alström syndrome, Batten disease, Joubert syndrome, peroxisomal diseases and Senior-Løken syndrome or other disease with similar presentation
3. Any contraindication to IVT injection, according to the Investigator's clinical judgment and international guidelines (Avery 2014)
4. Pregnant or breast-feeding female
5. Any clinically significant cardiac disease or defect, in the opinion of the Investigator
6. Personal or family history of prolonged QT syndrome or QTcF ≥ 450 ms (adult subjects and pediatric subjects >10 years old) or QTcB ≥ 450 ms (pediatric subjects ≤ 10 years old) by ECG at Screening

NOTE: Exclusion criteria 7 through 9 are related to acceptable laboratory values at Screening. Subjects with a screening laboratory value outside the specified range may be permitted if the value is not clinically significant in the opinion of the Investigator, with concurrence from the Sponsor's Medical Monitor.

7. Estimated Glomerular Filtration Rate (eGFR) less than the lower limit of normal.
8. AST or ALT greater than 1.2x the ULN
9. One or more coagulation parameters (platelet count, International Normalized Ratio [INR]) outside of the normal range
10. Any ocular disease or condition that could compromise treatment safety, visual acuity or interfere with assessment of efficacy and safety, as determined by the Investigator
11. Prior receipt of intraocular surgery or IVT injection within 3 months prior to study start or planned intraocular surgery or procedure during the course of the study
12. Use of any investigational drug or device within 90 days or 5 half-lives of Day 1, whichever is longer, or plans to participate in another study of a drug or device during the PQ-110-001 study period
13. Any prior receipt of genetic therapy for LCA

14. Any severe, acute or chronic medical or psychiatric condition, including substance abuse, laboratory abnormality or other condition that, in the judgment of the Investigator, would place the subject at undue risk, interfere with the results of the study, or make the subject otherwise unsuitable
15. History of malignancy within 5 years prior to Screening, except adequately treated cutaneous squamous or basal cell carcinoma

No waivers to the exclusion criteria are permitted.

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.

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. Used mixing vials containing residual study drug should be stored at 2º to 8º C for accountability by a Sponsor representative (monitor). In case of serious adverse events (SAEs), used vials may be collected by the Sponsor for endotoxin testing and/or testing for bacterial contamination may be arranged locally by 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

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), betablocker ophthalmic solutions, prostaglandin analog ophthalmic solutions, ophthalmic solutions/gels of corticosteroids, antibiotics and antiseptics, topical agents for pupillary dilatation, and antiallergic 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 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-110-001 study period is prohibited.

6.2.3 Adequate Forms of Birth Control

Women of child bearing potential (WOCBP) must agree to use a highly effective method of birth control from the list below (defined as those, alone or in combination, that result in a failure rate of less than 1% per year when used consistently and correctly). Double barrier methods (a combination of condom with cap, diaphragm, or sponge with spermicide) are not considered highly effective. Childbearing potential is defined as menarche and until post-menopausal for ≥ 1 year, unless permanently sterile. 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 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 outlined in the protocol. For those procedures for which a specific time point post dose is required (eg, PK blood draws), the protocol refers to nominal times. Actual times for such assessments are to be recorded in the source documentation and in the electronic Case Report Forms (eCRFs), and if any time points are missed, the reasons are also to be recorded. Recording of actual times is not required for assessments for which only a study visit and not a specific time is stated in the protocol.

Each study visit may take up to 1 day, or may be conducted in multiple consecutive days instead of 1 full day, at the discretion of the Investigator.

Visits 7 days post injections have a visit window of +/- 3 days. Visits 1 month and 2 months post injections have a visit window of +/- 7 days, and dosing visits have a visit window of +/- 10 days. The visit 14 days post-dose 1 is conducted by telephone and has a visit window of +/- 3 days.

7.2 Screening

Subject screening should be conducted ≤ 28 days prior to study drug dosing (Day 1). A screening log of all consented subjects will be kept at each study center.

During the screening period, subjects will be assessed according to the eligibility criteria and specified assessments conducted, as presented in the SOE . At the discretion of the Investigator, the feasibility of performing an IVT injection on the subject may be assessed using noninvasive methods, as outlined in the Study Reference Manual. Historic genotyping results from a certified laboratory are acceptable with Sponsor approval. For subjects without a historic genotyping result, genotyping and gene sequencing analysis to determine the presence of the *CEP290* p.Cys998X mutation will be performed. For all subjects, screening 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.

7.3 Dosing and Follow-up Visits

Dosing visits occur on Day 1 (Visit 2), Month 3 (Visit 8), Month 6 (Visit 13), and Month 9 (Visit 17). 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.

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

7.4 End of Study Visit

The EOS visit occurs 3 months after the 4th dose of study drug, Month 12 (Visit 21) for subjects who have not discontinued study drug. Subjects who discontinue study drug but do not withdraw study consent will continue to be followed for safety through the EOS visit (see Section 4.2.2.1). Subjects who discontinue study drug should complete: 1) study visits until the time of their next scheduled dose, and 2) the remaining visits of 3, 6, 9 and 12 months. All EOS assessments and procedures should be completed as indicated per the SOE

Subjects who discontinue the study (eg, withdraw consent) should have all assessments conducted at the EOS visit at the time of withdrawal, for safety monitoring purposes.

7.5 Follow-up Extension Study

An extension study, which would permit continued dosing of eligible subjects who complete PQ-110-001, do not meet stopping criteria in PQ-110-001 and derive therapeutic benefit, is planned. The sponsor will base the decision to open an extension study on the safety and efficacy data obtained during PQ-110-001 and the risk/benefit analysis for subjects.

8.0 STUDY ASSESSMENT PROCEDURES

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

8.1 Adverse Events

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

8.2 Vital Signs

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

8.3 Laboratory Evaluations

All laboratory evaluations will be conducted at a central laboratory, except Erythrocyte Sedimentation Rate (ESR), which will be conducted locally. Reference ranges for all laboratory parameters are provided in the Laboratory Manual.

Serum chemistries will include sodium, potassium, chloride, bicarbonate (or serum carbon dioxide), blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphorus, ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, uric acid, lactic dehydrogenase (LDH), albumin, total protein, triglycerides, and cholesterol. Estimated Glomerular Filtration Rate (eGFR) is to be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation 2009 calculation for adult subjects and Schwartz equation, according to the recommendation from National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), for pediatric subjects.

Hematology will include a complete blood count (CBC): CBC with absolute differential (hematocrit, hemoglobin, white blood count, red blood cell count, neutrophils, granulocytes, lymphocytes, monocytes, eosinophils, basophils, platelet count). Urinalysis (by visual inspection and dipstick) will include color and appearance, specific gravity, pH, protein, glucose, blood, ketones, bilirubin, leukocyte, nitrite, and urobilinogen. In addition, microscopic analyses will be performed on samples with abnormal dipstick results.

C4, Hemolytic complement 50 (CH50), INR, ESR and C Reactive Protein (CRP) will also be assessed.

For female subjects of child bearing potential, a serum pregnancy test is required at Screening. Urine pregnancy tests are acceptable for subsequent time points.

Subject eligibility is determined based on Screening laboratory values. If any relevant changes in the subject's medical history occur between Screening and Day 1, the Investigator should repeat laboratory assessments prior to the subject's first dose of study drug to confirm eligibility.

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 are eligibility criteria should be discussed with the Sponsor Medical Monitor prior to subject inclusion.

8.4 Pharmacokinetic Evaluations

Samples for PK analysis will be collected as indicated per the SOE

Blood samples will be obtained from all subjects to assess PK parameters of QR-110 ($AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, C_0, T_{max}, $T_{1/2}$, CL, V_d) pre- and post-dosing as indicated per the SOE (Appendix 1). $T_{1/2}$ and V_d will only be evaluated if measurable serum levels are obtained.

8.5 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 Sponsor Medical Monitor. Details on the conduct of ECGs is provided in the Study Reference Manual.

8.6 Physical Examination

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

8.7 Height and Weight

Height will be measured using a calibrated, wall-mounted stadiometer and will be documented as indicated per the SOE. Body weight will be measured using a calibrated scale as indicated per the SOE

8.8 Ophthalmic Exams

Ophthalmic examinations will be performed at all study visits. BCVA will also be assessed at specified time points as indicated per the SOE - The ophthalmic exam is comprised of: BCVA; 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; 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 National Institute of Health (NIH) Grading Scale for Vitreous Haze.

The procedures for ophthalmic exams are outlined in the Study Reference Manual.

8.9 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 DMC and Sponsor 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.

8.10 Leber's Congenital Amaurosis Genetic Analysis

Genotyping results (either historic or at screening) are required for eligibility. For subjects without an acceptable historic genotyping result, genotyping and sequencing of genes associated with inherited retinal dystrophies will be performed at Screening. Separate informed consent may need to be obtained per local requirements. A blood sample for genotyping and gene sequencing should be obtained at the Screening Visit.

8.11 Biomarkers

and stored for later quantification. In addition, blood samples for biomarkers may be collected at any study visit at which inflammation, pain or redness of the eye is present, including any unscheduled visits.

8.12 Efficacy Assessments

Subjects must perform all Screening examinations. If a subject is unable to perform a specific assessment at a subsequent visit, this should be recorded in the eCRF and the subject's ability reassessed at the next specified visit. All attempts at performing assessments should be recorded in the eCRF.

Most measures of visual function (BCVA, FST, mobility course, oculomotor instability, PLR) will be measured a minimum of 2 times prior to the subject's first dose of study drug to evaluate intrasubject variability (Screening and predose on Day 1). Measures of retinal anatomy (infrared imaging and OCT) and ERG will be measured a minimum of 1 time prior to the subject's first dose of study drug. Any predose 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. In the case of repeat assessments, the measure reflecting the average of the measures will be considered the Baseline value.

If possible, photoreceptor outer segment layer thickness will be calculated from OCT images as an exploratory 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.

Narratives will be written for all participating subjects on an ongoing basis.

Exploratory 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 Data Monitoring Committee

An independent DMC will provide safety oversight for the study. A DMC operational charter will be finalized and an initial organizational meeting held prior to screening of the first subject.

Once the first 2 adult subjects have been dosed and safety and tolerability data for at least 4 weeks post dose are available, the DMC will review safety and tolerability data, and provide their recommendation for proceeding to the next dosing cohort, as described in Section 4.2.2 and the DMC Charter.

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

An 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) (See 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

An 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

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

All significant medical conditions including signs/symptoms of the underlying diagnosis found during the screening period and up to initiation of dosing (Visit 2) will be captured as medical history. Any event/condition related to participation in the study or study procedures but not related to underlying or concomitant disease that is noted after Screening up to the date of first dose will be captured as a non-treatment emergent AE.

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

Adverse events and SAEs related to study drug that persist > 90 days 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 adverse events 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).

a. 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.

b. Persistent or Recurrent Adverse Events

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

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

c. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs on the eCRF 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.

d. Deaths

All deaths that occur during the protocol-specified AE reporting period (see 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.

e. Preexisting Medical Conditions

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

f. Hospitalization, Prolonged Hospitalization or Surgery

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

g. Pregnancy

If a female subject or a female partner of a male subject becomes pregnant while the female subject or the male partner is receiving study drug or within 6 months after the last dose of 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 (see 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.

h. 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 for the cohort assignment. 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 adverse events 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 Harmonisation (ICH) GCP E6, Section 4.11.1 (ICH 1996).

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 country requirements. All SUSARs will be reported as required to the Competent Authorities of all involved European member states.

- The Investigator will notify local IRB/EC of SUSARs or significant risks to subjects, per local country requirements. The Investigator must keep copies of all AE information, including correspondence with the Sponsor or local IRB/EC on file.

- All studies that are conducted within any European country will comply with the European Clinical Trial Directive 2005/28/EC, the Clinical Trial Directive 2001/20/EC and the Detailed Guidance CT-3 (2011/C 172/01).

10.0 STATISTICAL METHODOLOGY

10.1 General Considerations

A comprehensive Statistical Analysis Plan (SAP) specifies 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. As the risk profile of QR-110 in humans is unknown and this is a first-in-human trial, all AEs will be considered in determining the safety profile of QR-110 unless obviously unrelated. As an early phase clinical study, exploratory analyses not necessarily identified in the SAP may be performed to support the clinical development program. Any p values that will be calculated according to the analysis plan will be interpreted in view of the exploratory nature of the study. Any post-hoc, or unplanned, analyses not identified in the SAP will be clearly identified in the CSR, in accordance with applicable Standard Operating Procedures (SOPs) of the sponsor.

10.2 Determination of Sample Size

This is a Phase 1b/2 safety study designed to evaluate the safety, tolerability and PK of QR-110. The sample size is not based on power calculations. It is chosen based on clinical experience and considered to be adequate to fulfill the objectives of the study.

Twelve subjects are planned to be enrolled in the study. However, depending upon observed results, the DMC and Sponsor Medical Monitor may add subjects as indicated in Table 3 (Section 4.2.2.2), for a maximum number of subjects up to a total of N=18. The decision to add subjects is based on DMC and Sponsor Medical Monitor review of safety and tolerability and not based on efficacy; hence, exploratory efficacy analyses will not impact the DMC and Sponsor Medical Monitor review of accumulating safety data and the potential for additional subjects above 12.

10.2.1 Randomization and Blinding

No randomization or blinding is required for this study.

10.2.2 Replacement of Subjects

Subjects who discontinue from the study without receiving any study drug will be replaced. Subjects discontinuing the study before the full course of study drug may be replaced by a subject who will be assigned the same dose as the subject being replaced. The decision for replacement will be made by the Sponsor based on available data and perceived need for additional data.

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 subjects in the Efficacy Evaluable Population with the exception of subjects 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 (PK) 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. 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 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. The baseline data is defined as the data most recently collected and/or the average of the measures (eg, for ophthalmic assessments performed two or more times) prior to the first dose.

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 AE (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 sign 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 in the following ways:

- 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: $AUC_{0-\infty}=AUC_{last}+C_{last}(obs)/\lambda z$, 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 an elimination rate constant (λ_z) is estimable): Apparent volume of distribution at steady state of the drug will be determined from trough levels.

Serum concentration below 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, $AUC_{0\text{-tlast}}$, $AUC_{0-\infty}$, 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 $T_{½}$. 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 efficacy evaluations will include:

- Secondary efficacy evaluations
    - BCVA
    - FST
    - PLR
- Exploratory efficacy evaluations

Descriptive statistics of clinical efficacy will be tabulated by dose group, 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. 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.

Continuous efficacy endpoints will be summarized and may be analyzed using appropriate parametric or nonparametric inference tests.

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

10.9 Interim Analysis

Safety will be assessed prior to each dose escalation and prior to the enrollment of pediatric subjects by the DMC and Sponsor Medical Monitor. Efficacy exploratory reviews will be planned on a continuous basis.

10.10 Multiplicity Considerations

No multiplicity adjustments are planned in this exploratory Phase 1b/2 study.

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 Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations, before recording data on eCRFs. All corrections to eCRFs will be made by authorized users, and the changes will be automatically logged in the audit trail of the system (time and date stamps and the user entering or updating data). Electronic CRFs should be completed for every subject screened or enrolled in the study. 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.

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. Separate Informed Consent Forms may be required for gene sequencing, and/or biomarker testing. 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.

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 United States Food and Drug Administration (USFDA), 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

A coordinating Investigator for the PQ-110-001 study will be selected from the participating sites by the Sponsor.

13.1 Investigator's Brochure

Before the study begins, the Investigator will receive the QR-110 Investigator's Brochure (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, DMC, 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 GCP 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 European Competent Authorities and ECs when the study is terminated, within 90 days of the last subject's 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 visit for the last subject (LVLS) in the PQ-110-001 clinical study (Visit 21 or the End of Study Visit).

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