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Protocol PQ-110-002

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

Protocol Number: **(Version Date)**	Version 3.0 14 January 2019
Name of Test Drug:	QR-110 Solution for Intravitreal Injection
Phase:	1b/2
Methodology:	Open-label, extension study
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
Sponsor Representative:	
Document Date:	04 JAN 2022
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SIGNATURE PAGE

Protocol Title:	An Open-Label, Extension Study to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of QR-110 in Subjects with Leber's Congenital Amaurosis (LCA) due to the c.2991+1655A>G Mutation (p.Cys998X) in the *CEP290* Gene
Sponsor:	ProQR Therapeutics Zernikedreef 9 2333 CK Leiden The Netherlands
Protocol Number:	PQ-110-002
Document Date/Version:	16 Jun 2021, version 0.2

Signature:_____

Date:_____

Signature:_____

Date:_____

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Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:

Signature:_____

Date:_____

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LIST OF IN-TEXT TABLES

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ABBREVIATIONS

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

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Abbreviation	Definition
ETDRS	Early Treatment Diabetic Retinopathy Study
FST	Full-field Stimulus Testing (also, Full-field Stimulus Threshold Testing or Full-field Scotopic Threshold Testing)
HM	hand motion
ICH	International Council on Harmonisation
INR	international normalized ratio
IOP	intraocular pressure
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
NIH	National Institute of Health
NIRAF	near infrared autofluorescence
OCI	oculomotor instability
OCT	optical coherence tomography
ONL	outer nuclear layer
p.Cys998X	Protein product from the c.2991+1655A>G mutation in the *CEP290* gene
PK	pharmacokinetic
PLR	pupillary light reflex
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event
SEM	standard error of mean
SAP	statistical analysis plan
SOC	system organ class
SOE	schedule of events
SUN	Standardization of Uveitis Nomenclature

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Abbreviation	**Definition**
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$T_{1/2}$	terminal half-life
T_{max}	time of maximum concentration
ULN	upper limit of normal
US	United States
V_d	volume of distribution
VF	visual field
VFQ-25	Visual Function Questionnaire-25
WOCBP	women of childbearing potential

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1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

ProQR Therapeutics (ProQR) is developing an antisense oligonucleotide (AON) product, sepofarsen, for the treatment of patients with Leber congenital amaurosis (LCA) due to the c.2991+1655A>G (p.Cys998X) mutation in the Centrosomal Protein of 290kDa (CEP290) gene. Leber congenital amaurosis caused by mutations in the *CEP290* gene (ie, LCA type 10 [LCA10]) is a severe inherited retinal degenerative disease resulting in blindness, often in early childhood. There are currently no approved therapies for the treatment of LCA10 due to the c.2991 +1655A>G mutation and an important unmet medical need exists. The primary goal of the development plan for sepofarsen is to provide a treatment to overcome the genetic defect in patients with at least 1 *CEP290* allele containing the *CEP290* mutation, resulting in functional vision restoration or preservation. The intended route of administration is intravitreal (IVT) injection.

PQ-110-002 study is an open-label, extension study from study PQ-110-001, to evaluate the safety, tolerability, efficacy, and pharmacokinetics of sepofarsen in subjects with LCA due to c.2991+1655A>G mutation in the *CEP290* gene. PQ-110-001 was a 1b/2 phase, open-label, multiple dose, dose escalation study to evaluate the safety and tolerability of sepofarsen in subjects with LCA due to the above mentioned mutation.

1.2. Objectives of Statistical Analysis

This statistical analysis plan (SAP) describes the populations for analysis, data handling rules, statistical methods, and formats for data presentation that will be required for the analysis of data from trial PQ-110-002. The statistical analyses and summary tabulations that will be produced for the analysis as described in this SAP will provide the basis for the results sections of the interim and final clinical study

reports (CSRs) for this trial. The SAP will also outline any differences between the currently planned analyses and those specified in the clinical study protocol.

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2. STUDY DESIGN

2.1. Synopsis of Study Design

This study is an open-label, extension study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of sepofarsen in subjects with LCA due to c.2991 +1655A>G mutation in the *CEP290* gene.

Subjects will be given the opportunity to enroll into this extension study for continued dosing if available data support current and/or future benefits for the subject. The Investigator, in consultation and agreement with the Medical Monitor, will decide on enrollment of each individual subject, as well as on dosing of the first treated eye and treatment initiation of the contralateral eye. Continued subject treatment in this study is desirable, but cannot be guaranteed, since it will depend on the risks and benefit of further treatment on a case-by-case basis, as discussed and agreed upon with the Medical Monitor.

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

The contralateral eye and the first treated eye will be injected 3 months apart. The injection interval of 3 months between both eyes will limit burden for the subjects. This between-eye interval could be adapted if safety data are supportive, and for logistic reasons, and in agreement with the Medical Monitor. The same safety monitoring protocol and efficacy assessments will apply to both eyes.

2.2. Randomization Methodology

This is an open-label study; randomization is not required as the study is not randomized.

2.3. Stopping Rules and

The Investigator or the Medical Monitor may stop treatment for an individual subject due to an

AE. 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 sepofarsen and association with other safety signals or laboratory values should be considered in the decision to stop treatment. The Medical Monitor must be notified of any subject who stops treatment due to an AE. Adverse events considered to be related to the study drug should be taken into account in the benefit/risk assessment.

Subjects who discontinue study drug will be encouraged to remain in the study for observation for at least 3 months post last dose.

The Investigator and/or the Sponsor may decide to stop treatment for an individual subject due to an AE.

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

2.4. **Study Procedures**

The schedule of assessments, as outlined in the study protocol, is provided in

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Statistical Analysis Plan Template

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2.5. **Safety, Efficacy and Pharmacokinetic Endpoints**

2.5.1. **Safety Endpoints**

2.5.1.1. Primary Endpoint

The primary endpoints are:

- Frequency and severity of ocular AEs
- Frequency and severity of non-ocular AEs

2.5.2. **Efficacy Endpoints**

2.5.2.1. Secondary Endpoints

Secondary endpoints include:

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

- Change from baseline in Near Infrared AutoFluorescence (NIRAF)
- Pharmacokinetics: Characterize the PK profile of sepofarsen in serum

2.5.2.2. Exploratory Endpoints (at Investigator Discretion)

2.5.3. Pharmacokinetic Endpoints

It is expected that the vast majority of measured PK concentrations is below limit of quantification (BLQ). Thus, no pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-24}, AUC_{last} and AUC_{0-inf}) will be derived. All individual measurement results above limit of quantification will be shown in a individual level table, and all measurements – above or below limit of quantification will be presented in the listings.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- **All Screened Subjects**: All subjects who provided informed consent or assent document to participate in the study.
- **Safety Population**: All subjects who received any sepofarsen during study PQ-110-001 and were enrolled in this study.-
- **Efficacy Evaluable Population**: All subjects who received any sepofarsen with at least one baseline 002 and post-baseline 002 BCVA measurement.
- **Per Protocol Analysis Set:** All subjects in the Efficacy Evaluable Population, with the exception of subjects and/or data points with major protocol deviations affecting subjects and/or specific assessments within a subject (see Section 3.2). The list of major protocol deviations selected for exclusion from this analysis set will be completed prior to database lock.

The Safety Population is the primary population for the summaries of demographics, baseline disease characteristics, medical history, concomitant medications, major protocol deviations and all safety endpoints. The Efficacy Evaluable Population is the primary population for the analyses of all efficacy endpoints, where missing values will be reported for subjects that have missing values in their baseline measurements of that specific secondary endpoint. A subset of efficacy endpoints may be evaluated for the Per Protocol Population.

Unless otherwise stated, data presentations will be listed and summarized by treatment group.

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3.2. **Protocol Deviations**

Departures from the protocol will be classified as major or minor protocol deviations. The list of major protocol deviations, including those to be excluded from the per protocol analysis set, will be completed prior to database lock. The details of the protocol deviations will be described in a separate Protocol Deviation Plan.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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

4.2. General Statistical Methods and Data Handling

4.2.1. General Methods

All outputs will be incorporated into bookmarked PDFs and /or Microsoft Excel or Word files~~,~~ sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, safety and efficacy parameters. For continuous efficacy variables, the data will be summarized using the number of subjects, mean, standard deviation, standard error, median, minimum, maximum and 95% confidence intervals for the mean. For all other continuous variables, the data will be summarized using the mean, standard deviation, median, minimum and maximum. All categorical variables will be summarized by the number of subjects and percentage within each category (with a category for missing data, if any) of the parameter. For any categorical variable for an efficacy endpoint, summary tabulations of the variable will also include 95% confidence intervals for the percentage.

4.2.2. Treatment Groups for Analysis

Safety and efficacy data will be summarized by treatment group. The first treated eyes data will be summarized based on the treatment group allocation in study PQ-110-001. The subjects who started with 320/160 µg in study PQ-110-001 will be moved to 160/80 ug group in study PQ-110-002; other subjects who started with 160/80 µg in study PQ-110-001 will continue the same dose in study PQ-110-002. The contralateral eyes data will be summarized for treated and non-treated for the overall study

population in study PQ-110-002.

4.2.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coded using MedDRA Version 20.0. Concomitant medications will be coded using World Health Organization (WHO) Drug Global B3/C3-format March 1, 2021.

4.2.4. Definition of Baseline

For the endpoints collected on the subject level, the screening visit value in study PQ-110-002 will be defined as Baseline 002 values. For the endpoints collected on the eye level, there are three types of baseline values used for study PQ-110-002:

- Baseline 001: for BCVA, it is defined as

  for mobility course and FST, the average of measurements at pre-dose in study PQ-110-001 is considered as baseline 001.
- Baseline 002: for BCVA, it is defined as

  ; for mobility course and FST, it's defined as the average of last two measurements only if the interval between them is up to 1 month before entering study PQ-110-002. Otherwise the most recent value will be taken as baseline 002. For the other endpoints, the screening value in study PQ-110-002 is used as baseline 002 value.
- Pre-dose Baseline: the efficacy endpoints collected on the eye level except BCVA, mobility course and FST, the baseline 002 will be used. For BCVA, mobility course and FST , Baseline 001 values are used for the first treated eye, non-treated contralateral eye as well as both eyes. For treated contralateral eye,
  - For BCVA, the baseline result corresponds to the best of the two most recent BCVA values available before the first dose of treatment with sepofarsen in that respective eye

in study PQ-110-002 (in a maximum time-window of 1 month before dosing). If only one observation is available on or prior to the subject's first dose, that observation will be used as the pre-dose baseline value. For mobility course, FST and OCT, the data most recently collected prior to the subject's first dose of study treatment in study PQ-110-002 will be used as the pre-dose baseline value.

- For other efficacy endpoints collected on the eye level, the baseline 002 will be used.

4.2.5. Adjustments for Covariates

Adjustment for baseline BCVA will be applied for any inferential statistical analysis performed. If inferential statistical analysis will be requested at some point, this will be described in an addendum to this SAP.

4.2.6. Multiple Comparisons/Multiplicity

Adjustment for baseline BCVA will be applied for any inferential statistical analysis performed. If inferential statistical analysis will be requested at some point, this will be described in an addendum to this SAP.

4.2.7. Subpopulations

Subject-level summary tables will be generated featuring the following subpopulations:

- On-chart versus off-chart subjects. On-chart subjects are defined as subjects who can read letters on the ETDRS chart and for whom a logMAR value is available based on ETDRS in the logMAR category of < +1.7 logMAR. Off-chart subjects are defined as subjects who cannot read letters on the ETDRS chart and for whom a logMAR value is available based on BRVT in the logMAR category of ≥ +1.7 logMAR.
- Adult (≥ 18 years of age) versus pediatric (<18 years of age) subjects
- Blue minus red FST response > 2 log cd/m^2 versus blue minus red FST ≤2 log cd/m^2

4.2.8. **Discontinuations from Study Drug and Discontinuations from the Trial**

If the subject stops treatment for any reason, in general, the subject will be encouraged to remain in the study for observation for at least 3 months post last dose (see Protocol Section 4.2.2).

Subjects who discontinued from the trial will not be replaced as this is an extension study.

4.2.9. **Missing, Unused, and Spurious Data**

Missing data are defined as values that are not available and that would be meaningful for analysis if they were observed. Information that explains why data is missing data, including the relationship to COVID-19, will be captured in the electronic case report form and summarized in the clinical study report.

Missing data handling for mobility course composite score, BCVA and FST data is described in Section 4.2.9.1, 4.2.9.2. No imputation methods are planned for missing data for other efficacy endpoints or for safety data, except for partial or missing dates for the start and end of adverse events and for the use of concomitant medications, as described in Sections 4.2.9.3 and 4.2.9.4. The planned approach to handle partial and missing start dates for AEs and concomitant medications is conservative, in that the imputation is designed to impute a start date to occur within the period following the first dose of study treatment, rather than in the screening period. The planned approach to impute partial and missing end dates for AEs and concomitant medications is also conservative, as the imputed dates are fixed at the latest plausible date given the available information for that data record and the timing of the individual subject's visits.

4.2.9.1 Missing data in Central Reading Center Mobility Course Composite Score

Missing course composite scores from the central reading center will be imputed as follows for the mobility course analyses:

- The reading center may not receive a video of the subject navigation attempt, or the video of the navigation attempt may be marginalized due to technical error, resulting in an inability to grade the navigation attempt. Marginalization of a video can occur due to lack of infra-red (IR) used on one or both cameras, truncated recording on one or both cameras, or one or both cameras recording out

of focus. In these instances, the reading center graders cannot grade the video with maximum accuracy, resulting in missing data, and the site score will be used to impute the central reading center score.

- An error in site level grading results in the early termination of the mobility test, before a pass occurs: The site technicians may grade the navigation attempt a "pass" and conclude the test prematurely (no video available), whereas the review from the reading center may identify the final navigation attempt as a "fail". Therefore, a passing light level would not be identified by the reading center, resulting in missing data. In this case the following imputations will be used:
    - Last observation carried forward within the given eye (OD, OS, or OU) from prior visit.
    - In the event that imputing the last observation carried forward would result in the imputation of a pre-treatment score to a post-treatment time point, the following imputation will be used: the site level course composite score minus 1. This is the next easiest course / light level score. The next easiest score is defined as the score associated with passing the subsequent light level that would have been tested had the site correctly graded the navigation test as a fail and continued testing at the next light level. If, after the above imputations are applied, the composite score is still missing (e.g., for other reasons such as a visit not having been conducted), then the composite score will be treated as missing for analysis.

4.2.9.2 Missing BCVA and FST Data

If a subject stops treatment of study drug for any reason before end of trial, in general, the subject will remain in the trial and BCVA and FST data will be available and used as is in the calculations.

If a subject has no measurement within the defined visit window the value measured closest to the window will be taken.

Data will be imputed if the subject has missing BCVA and FST for any of the following reasons:

- a subject withdraws consent for unknown reasons or related to the medical procedure.
- a subject withdraws consent for reasons unrelated to the medical procedure as elicited at the end of study/early termination visit, or the subject dies from an unrelated event.

The following imputation methods will be used:

- **All-last observation carry-forward (ALL-LOCF):** All missing data of the endpoint is imputed by the respective last observation carry forward method.
- **All-baseline carry-forward (ALL-BOCF)**: All missing data of the endpoint is imputed by the respective baseline value of the subject.

For the handling of missing values for the Month 12 BCVA data, two analysis will be performed as below:

- No imputation method will be used and analyze all available BCVA data.
- For the subjects with at least one ongoing AE of cataract or retinal (CME) adverse events, Month 12 assessment BCVA data will be considered as missing data and imputed using All-LOCF.

4.2.9.3 Partial and Missing Data for Adverse Events

*4.2.9.3.1 **Partial and Missing AE Start Dates***

If an AE start date is completely missing, and either the available (complete, partial) AE end date/time information indicates that the AE ended before the date/time of first dosing of study treatment on Day 1 or the subject did not receive study treatment, impute the AE start date as the date of informed consent and consider the adverse event as non-treatment-emergent.

If an AE start date is completely missing, the subject received study treatment, and either the AE end date information is completely missing or the available AE end date/time information indicates that the AE did not end before the date/time of first dosing of study treatment on Day 1, impute the AE start date to Day 1. The adverse event will be assumed to be treatment-emergent following the first dose of study treatment.

If a partial AE start date is consistent with the actual start date being on Day 1, and either the AE end date information is completely missing, or the complete or imputed AE end date/time information indicates that the AE did not end before Day 1, the imputed AE start date will be Day 1 in the following scenarios:

- The AE start time is missing (the adverse event will be flagged as treatment-emergent following the first dose of study treatment)
- The AE start time is after the date/time of first dosing of study treatment on Day 1 (the adverse event will be flagged as treatment-emergent following the first dose of study treatment)
- The AE start time is before the time of first dosing of study treatment on Day 1, and imputing the AE start date as Day 2 instead of Day 1 would be inconsistent with the partially recorded AE start date (e.g., the calendar month for Day 2 is not the same as for Day 1), or with the complete or imputed AE end date/time (in this case, the adverse event will not be flagged as treatment-emergent following the first dose of study treatment).

Otherwise, if the start date for an AE is partially recorded, the AE start date will be imputed as the date of first dose of study treatment, and the adverse event will be considered treatment emergent.

*4.2.9.3.2. **Partial and Missing AE End Dates***

If the end date for an AE is completely missing, the Adverse event will be assumed to be ongoing on the date of the subject's last visit. If the end date for an AE is partially recorded, then the AE end date will be re-imputed as the date of the subject's last visit.

4.2.9.4 Partial and Missing Dates for Concomitant Medications

*4.2.9.4.1 **Partial and Missing Start Dates for Concomitant Medications***

If a medication start date is completely missing, the medication start date will be imputed as the date of informed consent.

If a partial medication start date is consistent with occurring on Day 1, the subject received study treatment, and the available medication end date information indicates that the medication did not end before Day 1, the imputed medication start date will be Day 1.

Otherwise, if the medication start date is partially recorded, the medication start date will be imputed as follows:

- The first day of the month if day is missing
- January if month is missing
- If only year is recorded, 1 January

If medication start date imputed in this way is before the date of the subject's informed consent, the medication start date will be re-imputed as the date of the informed consent.

4.2.9.4.2. ***Partial and Missing End Dates for Concomitant Medications***

If the end date for a medication is completely missing, the end date will be imputed as the date of the subject's last visit. If the end date for a medication is partially recorded, the medication end date will be imputed as follows:

- The last day of the month if day is missing
- December if month is missing
- If only year is recorded, 31 December

If a medication end date imputed in this way is after the date of the subject's last visit, the medication end date will be re-imputed as the date of the subject's last visit.

4.2.10. **Visit Windows**

All visits should occur at the scheduled visits according to the schedule of events Section 2.4), but unscheduled visits may be necessary and visits to be performed at scheduled time points may be

performed later or earlier than planned in the protocol. All data to be summarized over time will be tabulated by visit, based on the schedule of events.

The Screening/ Day 1 visit should be the last visit of study PQ-110-001, ie, all Screening/Day 1 assessments should take place during the EOS visit of study PQ-110-001. If these visits do not occur at the same time, a separate Screening/Day 1 visit should be performed as part of PQ-110-002. Dosing visits occur on Day 1 for the contralateral eye and then every 6 months. Dosing visits for the previously (first) treated eye will occur 3 months after the dosing visit for the contralateral eye and then every 6 months. Study center phone calls to the subjects will occur 7 days post-IVT injection, ±3 days. The End of Study (EOS) visit occurs 3 months after the last dose of study drug for a subject.

For each visit, a visit window will establish a time interval around which data from the scheduled visit and any unscheduled visits will be considered to determine which data within the visit window should be summarized. In general, the visit window is the scheduled visit day +/-30 days. In exceptional cases, eg. related to the significant restrictions in site activities or subject's ability to travel to sites for visits as occurring related to the COVID-19 pandemic, extensions of the visit window or alterations in the schedule of event can be approved by the Medical Monitor. Such extensions of the visit window will be documented as protocol deviations. Still, sites should make every reasonable effort to complete scheduled visits within the time windows defined in the protocol.

Actual dates and times will be used for pharmacokinetic analyses rather than nominal days and times.

4.3. Interim Analyses

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

4.4. Subject Disposition

A tabulation of subject disposition will be presented by treatment group, age category and all subjects combined. Subject disposition will be summarized for All Screened Subjects, including the number

screened, the number screened failure, the number who received study drug in the first treated eye and contralateral eye, the number in each subject population for analysis, the number that discontinued study drug, and the number that discontinued the study, and the reasons for study discontinuation.

The same disposition summary described above will be also provided for the Safety Population.

A by-subject listing of study completion information, including the reason for premature study discontinuation, will be presented.

4.5. **Drug Exposure**

The summary of exposure to study drug will be presented by treatment group for the Safety Population. The exposure summary will summarize administration of study treatment to the first treatment eye, and the contralateral eye. The summary will include the number of doses received, the duration of treatment, the duration of follow up post first dose, the duration of follow-up post last dose, the cumulative dose, and the average daily dose, which will be calculated as follows:

- Duration of Treatment = date of last dose-date of first dose+1
- Total Duration of Follow Up Post First Dose = date of last assessment - date of first dose+1
- Duration of Follow Up Post Last Dose = date of last assessment – date of last dose+1
- Cumulative Dose = sum of all doses received
- Average Daily Dose = cumulative dose ÷ duration of follow up post first dose

The number of doses received will be summarized as a categorical variable, with the following categories, and the categires may be changed as per the available data:

- 1, 2, 3, 4, 5, 6 or 7 doses for summaries of exposure in the treatment eye
- 1, 2, 3, 4, 5, 6 or 7 doses for summaries of exposure in the contralateral eye

Listings of study drug exposure and compliance will be provided based on the Safety Population.

4.6. **Demographic and Baseline Characteristics**

Subject demographics and baseline 001 and 002 characteristics information for the Safety Population will be summarized by treatment group, age category and all subjects combined using descriptive statistics. No formal statistical comparisons will be performed.

Subject characteristics at baseline include age (as recorded on the eCRF), age category (<18 years, ≥18 years older), gender, race, ethnicity, body weight, height and Body Mass Index (BMI) as well as genotype for *CEP290* c. 2991+1655A>G (homozygous, compound heterozygous). The following formulae will be used to calculate BMI:

> Body Mass Index (BMI)= kg/m^2 (where kg is a person's weight in kilograms and m^2 is height in meters squared)

Baseline 001 and 002 disease characteristics include ophthalmic examinations, measurements and tests and BCVA (logMAR) (with separate categories for BCVA based on the Holladay and on the Lange equivalency table, in case of subjects for whom BCVA values could only be obtained via the clinical practice assessment).

Demographic and baseline characteristics data will also be provided in a by subject data listing.

A summary of non-ocular medical history and ocular medical history will be provided for the Safety Population. Non-ocular and ocular medical history will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Non-ocular and ocular medical will be summarized separately, by treatment group and for all subjects combined, SOC and PT. If a subject has multiple non-ocular or ocular history records which are coded to the same PT within the same SOC, that PT for that subject will only be reported once. The same applies if a subject has multiple non-ocular or ocular history records which are coded to the different PTs within the same SOC, that SOC will only be reported once for that subject.

Ocular and non-ocular medical history will also be listed separately using by-subject listings which will include medical and surgical history, date of onset and the date of resolution or ongoing status.

4.7. Safety Analyses

All reporting of safety data will be based on the Safety Population. Listings will include all available data.

4.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Adverse events are summarized by subject frequencies, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term).

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

The number and percentage of subjects with any TEAE, with any TEAEs assessed by the Investigator as related to study drug and those related to drug administration (definite, probable, or possible relationship), and with any serious adverse event will be summarized by treatment group and overall. Deaths, TEAE severity, seriousness, outcomes (resolved, resolved with sequelae, not resolved, resolving, fatal and unknown) and study discontinuation due to TEAE will also be tabulated by treatment group. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most severe occurrence) to each of the counts in the descriptive analysis, regardless of the number of episodes. No formal hypothesis-testing analysis of adverse events will be performed.

Missing or partial start and end dates will be imputed as described in Section 4.2.9.3 before determining whether an AE is treatment emergent. For subjects with an actual or imputed AE start date on Day 1, the

AE is treatment-emergent if the AE start time was not recorded or was after the time of the first dosing of study treatment on Day 1.

An ocular TEAE following the first dose of study treatment is an ocular adverse event that was not present prior to administration of the first dose of study treatment but was present after the first dose, or an event with onset prior to the first dose with an exacerbation of the event after the first dose.

A non-ocular TEAE is a non-ocular adverse event with onset after the first dose of study treatment, or an event that was present prior to the first dose which had an exacerbation (worsening) occurring after the first dose.

If an ocular TEAE affects both eyes, it will be listed and summarized as two ocular TEAEs, affecting the first treated and contralateral eye. If a subject has multiple TEAEs which are coded to the same PT within the same SOC, that PT will only be reported once for that subject. Similarly, if a subject has multiple TEAEs which are coded to different PTs within the same SOC, that SOC will only be reported once for that subject.

In summaries of TEAEs by relationship, if there is more than one occurrence of a particular event for a subject, the event of most related will be included in the summary tables of TEAEs. In addition to presenting TEAEs by each relationship category (possibly related, probably related, and definitely related), as indicated for the event by the Investigator, TEAEs will be summarized by the categories as being either related or not related, where an TEAE will be considered related to study treatment if the event is at least 'possibly' related (i.e., to include 'possibly related', 'probably related' and 'definitely related') or if the relationship is missing.

In summaries of TEAEs by severity, if there is more than one occurrence of a particular event for a subject, the event of greatest severity will be included in the summary tables of TEAEs. In summaries of TEAEs by both severity and relationship, the most severe of the TEAEs will be included in the summary tables of TEAEs.

Unless otherwise stated, the following summaries of TEAEs will be presented for all non-ocular TEAEs, and separately for ocular TEAEs in the first treated eye , in the treated contralateral eye before the first dose in the study , in the treated contralaertal eye after the first dose in the study and in the non-treated contralateral eye. Unless otherwise stated, any summary of any type of TEAEs or serious adverse events (SAEs) which includes the SOC and PT of the events, will order the SOC and the PTs within the SOC in alphabetical order.

The tables that provide an overview of TEAEs will be presented by treatment group, to include the number (and percentage) of subjects who had any TEAE, SAE, TEAE leading to discontinuation from study treatment, TEAE leading to discontinuation from the trial, deaths and will summarize the number of subjects who had a TEAE by severity, by relationship to study treatment and by relationship to study treatment administration.

The adverse events that were identified by the Investigator as meeting the definition of an adverse event of special interest (AESI), as defined in Section 9.2.4 of the clinical study protocol will be supplemented by events for which and AESI has been defined but for which are not meeting the criterion for an AESI.

The following summary tables will be produced:

- Overview of Non-ocular TEAEs
- Overview of Ocular TEAEs
- Non-ocular TEAEs by, SOC and PT
- Treatment-emergent AESIs
- Non-ocular TEAEs by Severity
- Ocular TEAEs by Severity
- Non-ocular TEAEs by Relationship to Study Treatment
- Ocular TEAEs by Relationship to Study Treatment
- Non-Ocular TEAEs by Severity and Relationship to Study Treatment
- Ocular TEAEs by Severity and Relationship to Study Treatment

- Non-ocular TEAEs by Relationship to Study Treatment Administration
- Ocular TEAEs by Relationship to study Treatment Administration
- Non-ocular TEAEs by Severity and Relationship to Study Treatment Administration
- Ocular TEAEs by Severity and Relationship to study Treatment Administration
- Non-ocular Treatment-emergent SAEs
- Ocular Treatment-emergent SAEs
- Non-OcularTEAEs Leading to Discontinuation from Study Treatment
- Ocular TEAEs Leading to Discontinuation from Study Treatment
- Non-Ocular TEAEs Leading to Discontinuation from the Study
- Ocular TEAEs Leading to Discontinuation from the Study

Listings for AEs, and SAEs will be generated separately for ocular and non-ocular events. A listing of AESIs will be provided, as well as a listing of AESIs as defined in the protocol for events that do not meet the criteria for an AESI . Additionally, listings of AEs leading to death will be generated.

4.7.2. Laboratory Data

Observed values and change from baseline in each hematology and clinical chemistry parameter will be summarized by treatment group, age category and scheduled study visit by using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) for the continuous data and frequencies and percentages for the categorical data.

Hematology, clinical chemistry and urinalysis data, and changes from baseline, will be presented in subject listings.

4.7.3. Vital Signs and Physical Examinations

Vital signs measurements will consist of height, weight, heart rate, blood pressure and oral 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 treatment group.

By-subject listings of vital signs data and complete and symptom-directed physical examinations (urogenital exams not required) findings will be presented in a data listing.

4.7.4. Electrocardiogram

12-lead electrocardiogram (ECG) data will be presented in a listing.

4.7.5. Ophthalmic Examination

A single summary and listing will be generated to summarize the slit-lamp bio-microscopy examination, lens opacity grading, intraocular pressure (IOP) monitoring and dilated fundus examinations. Data will be summarized by treatment group (see Section 4.2.2), eye (first treated eye contralateral eye and non-contralateral eye) and visit using continuous and categorical summary statistics.

4.7.5.1. Slit-Lamp Bio-microscopy Examinations

Slit-lamp bio-microscopy examinations of the eyelid/lashes, conjunctiva palpebral, conjunctiva bulbar, cornea, iris, anterior chamber, anterior chamber cells, anterior chamber flare, and lens examination will be summarized by treatment group, eye (first treated eye and contralateral eye) and visit. With the exception of presence of hypopyon (recorded as Yes, No), anterior chamber cells, and anterior chamber flare, the results will be graded as normal, abnormal not clinically significant or abnormal clinically significant. Results for assessments of anterior chamber cells will be recorded as 0 (no cells / <1), 0.5+ or trace (1 5 cells), 1+ (6 15 cells), 2+ (16 25 cells), 3+ (26 50 cells), or 4+ (>50 cells), and anterior chamber flare recorded using the Standardization of Uveitis Nomenclature (SUN) Working Group Grading Scheme: 0 (none), 1+ (faint), 2+ (moderate / iris and lens details clear), 3+ (marked / iris and lens details hazy), or 4+ (intense/ fibrin or plastic aqueous).

4.7.5.2. Cataract (Lens Opacity) – Grading

Nuclear opacity, cortical opacity and posterior subcapsular opacity will be graded using the Age-Related Eye Disease Study (AREDS) lens grading system on a 7-unit scale (<1, 1, 1.5, 2, 2.5, 3, >3).

4.7.5.3. Dilated Fundus Examinations

A dilated fundus examination of the vitreous, vitreous cells, vitreous flare/haze, macula, optic nerve, peripheral retina, choroid and cup-to-disc ratio will be performed at each visit. Except for vitreous flare/haze, vitreous cells and cup-to-disc ratio, the results will be graded as normal, abnormal not clinically significant or abnormal clinically significant. Grading of vitreous flare/haze and vitreous cells will follow the National Eye Institute Grading System. For vitreous flare/haze, the results will be recorded as 0 (clear, no inflammation present), 0.5+ (trace inflammation present), 1+ (few opacities, mild blurring, clear optic disc and vessels), 2+ (significant blurring, hazy optic disc and vessels), 3+ (optic disc visible, no vessels seen), 4+ (dense opacity obscures optic disc, optic disc not visible). For vitreous cells, the results will be recorded as 0 (0-cells), 0.5+ (1-10cells), 1+ (11-20cells), 2+ (20-30cells), 3+ (30-100cells), or 4+ (>100 cells). Cup-to-disc ratio will be assessed in the dilated fundus examination on a 0.1 to 1.0 scale in increments of 0.1.

4.7.5.4. Intraocular Pressure

Intraocular pressure (IOP) will be measured in each eye by the examiner (different equipments might be used between visits) and the results will be recorded in mmHg at screening, dosing and follow -up visits.

4.7.6. Optical Coherence Tomograph (OCT)

Optical coherence tomography (OCT) will measure full retinal thickness (FRT), outer nuclear layer (ONL) thickness, presence of macular edema, and photoreceptor outer segment layer thickness (PROST) performed by an independent reading center according to the schedule of events (Section 2.4
The OCT values will be summarized by treatment group, eye and visit for the Safety Population using continuous descriptive statistics or categorical descriptive statistics. OCT data and any comments that may be relevant to the OCT grading will be listed for each subject in the Safety Population. The measures listed

below, regardless of confidence score (high confidence, adequate confidence, inadequate confidence) will be used for summaries and listings.

The following categorical data are collected as part of the OCT assessments:

- Confidence Score
- Confidence Score Reason
- Presence of Cystoid Macular Edema
- Additional Retina Morphology on Any Scan:
- Vitreous Debris/Cells
- Epiretinal Membrane
- Normal Retina/Fovea Contour
- Retinal Striae
- Foveal Distortion
- Adverse event of special interest (AESI) parameters

- Final AESI determination
- AESI comments OCT related comments

The following continuous data are collected as part of the OCT assessments, and are measured in mm:

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Descriptive statistics will be provided in summary tables, along with counts of missing values, characterized as either 'cannot grade' or 'not applicable'. A listing of all available data (quantitative values and qualitative replies of 'cannot grade' or 'not applicable' will also be provided.

4.7.7. Prior and / or Concomitant Medications

Medications administered to subjects during the study will be categorized as prior and/or concomitant medication. If usage of a medication stopped before the administration of the first dose of study treatment, it will be counted as a prior medication.

Two definitions of concomitant medications are required for this study:

A concomitant medication for the first treated eye will either have started prior to first dosing in the first treated eye and is defined as a 'prior and concomitant medication for the first treated eye', or will have started after first dosing in the first treated eye and is defined as a 'concomitant medication for the first treated eye'.

A concomitant medication for the treated and non-treated contralateral eye will either have started prior to first dosing in the contralateral eye and is defined as a 'prior and concomitant medication for the contralateral eye', or will have started after first dosing in the contralateral eye and is defined as a 'concomitant medication for the contralateral eye'.

Missing or partial start and end dates will be imputed as described in Section 4.2.9.4 before identifying whether to classify medication usage as prior or the two categories of concomitant medication.

Medications will be coded using the WHO Drug Global B3/C3-format March 1, 2021. Prior and concomitant medication usage by subjects in the Safety Population will be summarized. The summaries will be tabulated by treatment group, Anatomic Therapeutic Class (ATC) and preferred term, and will be presented separately for ocular and non-ocular concomitant medication usage.

The listing of prior and concomitant medication usage will identify whether the medication was ocular or non-ocular and, for ocular medication, whether the medication was a prior medication, a concomitant medication for the first treated eye starting prior to or after first dose of study treatment, or a concomitant medication for the contralateral eye starting prior to or after first dose of study treatment in the contralateral eye.

4.8. **Efficacy Evaluation**

Descriptive statistics of efficacy endpoints (Section 2.5.2) will be tabulated by treatment group, age category, and if appropriate, for treatment groups combined. The efficacy analysis will be conducted using the Efficacy Evaluable Population and Per Protocol Analysis Set. If Per Protocol Analysis Set is identical to the Efficacy Evaluable Analysis Population, the analysis results are only reported for Efficacy Evaluable Analysis Population.

4.8.1. **BCVA**

The BCVA will be assessed using the BRVT and the ETDRS acuity test. The best BCVA reading (ie, smallest numerical value in logMAR) for the first treated eye (based on ETDRS/BRVT) at Screening is considered the baseline BCVA (see also Section 4.2.4).

BCVA is assessed using an ETDRS chart, or the BRVT (Bailey et al, 2012). ETDRS provides logMAR values using on-chart assessments (i.e., logMAR values < +1.7). BRVT provides logMAR values based on off-chart assessments (i.e., logMAR values ≥ +1.7), which is meant for subjects who cannot read letters.

For subjects whose vision cannot be assessed with BRVT Single Tumbling E or Grating Acuity charts yielding logMAR values, the following BCVA measures can be provided based on BRVT: white field projection (WFP) and black and white discrimination (BWD). The measures of WFP and BWD represent more qualitative levels of vision as described by Bailey et al. 2012. For this study, imputed logMAR values will be used for WFP and BWD, as outlined in Table 2. For subjects with vision equal or worse than light perception (LP) data can be collected through the clinical practice assessment

When a BCVA assessment is performed, the assessment by ETDRS is completed first and, for 'off-chart' subjects (for whom ETDRS yields no results), will be followed by assessment of counting fingers (CF), hand movement (HM) and light perception (LP), performed as per clinical practice (not BRVT) and, subsequently, by BRVT assessment. Data based on ETDRS or BRVT will be the primary data used for analysis. If a logMAR value is available from both ETDRS and BRVT, only the ETDRS result will be used for analysis.

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4.8.1.1. Descriptive Statistics and Listings

The mean observed value and change from baseline in logMAR values for BCVA based on ETDRS and BRVT will be summarized by treatment group, eye (first treated eye, treated contralateral eye, non-treated contralateral eye) and visit using continuous descriptive statistics on the logMAR scale for BCVA, using the Efficacy Evaluable Population. A second table with individual observed values and change from baseline over time will also be produced. In case subjects have individual BCVA responses based only on the clinical practice assessment, the corresponding logMAR values to be presented in the table will be based on both the Holladay equivalency table and the Lange equivalency table as described in Section 4.8.1.

Descriptive summaries of BCVA for the subpopulations of subjects defined in Section 4.2.7 will also be provided.

A subject listing of visual acuity (BCVA), including all available data will be produced for the Efficacy Evaluable Population, including both the actual value and change from baseline at post-baseline time points.

4.8.1.2. Responder Analysis for Treated Contralateral Eye

A responder analysis will be summarized on overall group and performed on all contralateral eyes treated in PQ-110-002 with the following definitions of responders:

- BCVA change from baseline for on-chart subjects (ie, BCVA < 1.7 logMAR based on ETDRS):
  - Equal or better than -0.2 logMAR, smaller values are better
  - Equal or better than -0.3 logMAR, smaller values are better
- BCVA change from baseline for off-chart subjects (ie, BCVA ≥ 1.7 logMAR based on BRVT/clinical practice assessment):
  - leading to a categorical change in VA category according to Holladay VA reference scale (Section 8):
    - From LP to HM or better, ie,
      - from logMAR 4 (clinical assessment) or logMAR 3.5 (BWD result from BRVT) to logMAR 3 (clinical assessment) or better (BRVT)
      - from logMAR 3.2 (WFP result from BRVT) to logMAR 2.9 or better (BRVT)
    - From HM to CF or better, ie,:
      - from logMAR 3 (if only clinical assessment result available) to logMAR 2 (if only clinical assessment result is available) or better (BRVT), OR:

- from logMAR 3 (if only clinical assessment result available) to logMAR 1.7 - 2 or better (BRVT), OR:
- from logMAR >2 – 2.9 (based on BRVT) to logMAR 1.7 - 2 or better (based on BRVT), AND the BCVA change from baseline is equal or better than -0.3 logMAR (ie, ≤ -0.3 logMAR)

o From CF to on-chart, ie,:

- from logMAR 2 (if only clinical assessment result available) to a logMAR value of < 1.7 based on ETDRS
- from logMAR 1.7 - 2 (based on BRVT) to a logMAR value of < 1.7 based on ETDRS AND the BCVA change from baseline is equal or better than -0.3 logMAR (ie, ≤ -0.3 logMAR)

• leading to a change in VA category according to Lange VA reference scale (Section 9)

o From LP to HM or better, ie:

- from logMAR >2.5 - 2.7 (based on BRVT/clinical assessment) to >2 - 2.5 (based on BRVT/clinical assessment) AND the BCVA change from baseline is equal or better than -0.3 logMAR (ie, ≤ -0.3 logMAR)

o From HM to CF, ie,:

- from logMAR 2.3 (if only clinical assessment result available) to logMAR 1.7 - 2 or better (based on BRVT), OR:
- from logMAR >2 - 2.5 (based on BRVT) to logMAR 1.7 - 2 or better (based on BRVT), AND the BCVA change from baseline is equal or better than -0.3 logMAR (ie, ≤ -0.3 logMAR)

o From CF to on-chart, ie,:

- from logMAR 2 (if only clinical assessment result available) to a logMAR value of < 1.7 based on ETDRS
- from logMAR 1.7-2 (based on BRVT) to a logMAR value of < 1.7 based on ETDRS AND the BCVA change from baseline is equal or better than -0.3 logMAR (ie, ≤ -0.3 logMAR)

4.8.1.3. Vision Preservation Analysis for the First Treated Eyes

A vision preservation analysis will be summarized on overall group and performed on the first treated eyes which were treated in PQ-110-001 and continue to be treated in PQ-110-002 with the following definitions of achieving the vision preservation:

- BCVA change from baseline for on-chart subjects (ie, BCVA < 1.7 logMAR based on ETDRS):
  - Among the subjects that are responders at month 12 to the -0.3 criterion
    - Remain responsders at -0.3 logMAR
    - Remain responsders at -0.2 logMAR (allowing a worsening of + 0.1 log MAR)
    - Have a worsening of equal or more than + 0.2 log MAR
    - Have a worsening of equal or more than + 0.3 log MAR
  - Among the subjects that are responders at month 12 to the -0.2 criterion
    - Remain responsders at -0.2 logMAR
    - Have a worsening of equal or more than + 0.1 log MAR
    - Have a worsening of equal or more than + 0.2 log MAR
    - Have a worsening of equal or more than + 0.3 log MAR

- BCVA change from baseline for off-chart subjects (ie, BCVA ≥ 1.7 logMAR based on BRVT/clinical practice assessment): leading to a categorical change in VA category according to Holladay VA reference scale (Section 8) or Lange VA reference scale (Section 9)
    - Among the subjects that are responders at month 12 to the responder criterion defined in the section 4.8.1.2, the same rule used for on-chart subjects will be performed.

4.8.2. **Mobility Course**

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4.8.3. **Full-Field Stimulus Threshold Testing (FST)**

Full field stimulus testing captures threshold measurements for each stimulus (blue and red light). Measurements with a Fail value of "0" are successful, and any measurements with a Fail value of "1" are unsuccessful. If the threshold value fails, the next successful value will be captured. FST thresholds will be measured by an independent reading center according to the schedule of events in section 2.4 and the Imaging Charter.

The mean FST values (i.e., light sensitivity) for each eye (first treated eye, treated and non-treated contralateral eye) will be summarized using continuous descriptive statistics by treatment group, eye and visit for each stimulus color, for all subjects in the Efficacy Evaluable Population. The FST values are the average of all FST stimulus sizes (in log cd/m^2) for the given eye at a given visit and stimulus color. Descriptive statistics will be based on only successful thresholds ('acceptable data').

A responder analysis will be performed on the contralateral eyes treated in PQ-110-002 with the following definitions of responders:

- Blue FST change from baseline:
  - Equal or better than -0.7 log (cd/ m^2), smaller values are better
  - Equal or better than -0.5 log (cd/ m^2), smaller values are better
- Red FST change from baseline:

- Equal or better than -0.7 log (cd/ m^2), smaller values are better
- Equal or better than -0.5 log (cd/ m^2), smaller values are better

A vision preservation analysis for FST will be performed the first treated eyes which were treated in PQ-110-001 and continue to be treated in PQ-110-002 with the following definitions of achieving the vision preservation:

- Blue FST change from baseline:
  - Among the subjects that are responders at month 12 to the -0.7 criterion
    - Remain responsders at -0.7 log (cd/ m^2)
    - Remain responsders at -0.6 log (cd/ m^2) (allowing a worsening of + 0.1 log (cd/ m^2))
    - Remain responsders at -0.5 log (cd/ m^2) (allowing a worsening of + 0.2 log (cd/ m^2))
    - Have a worsening of equal or more than + 0.3 log (cd/ m^2)
  - Among the subjects that are responders at month 12 to the -0.5 criterion
    - Remain responsders at -0. 5 log (cd/ m^2)
    - Have a worsening of equal or more than + 0.1 log (cd/ m^2)
    - Have a worsening of equal or more than + 0.2 log (cd/ m^2)
    - Have a worsening of equal or more than + 0.3 log (cd/ m^2)
- Red FST change from baseline:
  - Among the subjects that are responders at month 12 to the -0.7 criterion
    - Remain responsders at -0.7 log (cd/ m^2)
    - Remain responsders at -0.6 log (cd/ m^2) (allowing a worsening of + 0.1 log (cd/ m^2))
    - Remain responsders at -0.5 log (cd/ m^2) (allowing a worsening of + 0.2 log (cd/ m^2))

- Have a worsening of equal or more than + 0.3 log (cd/ m^2)

- Among the subjects that are responders at month 12 to the -0.5 criterion
  - Remain responsders at -0. 5 log (cd/ m^2)
  - Have a worsening of equal or more than + 0.1 log (cd/ m^2)
  - Have a worsening of equal or more than + 0.2 log (cd/ m^2)
  - Have a worsening of equal or more than + 0.3 log (cd/ m^2)

In addition, tables with individual values over time will also be produced, for both original and change from baseline values. A subject listing of all failed and successful threshold FST, including FST related comments will be produced for the Efficacy Evaluable Population.

4.8.4. **Optical Coherence Testing**

OCT parameters related to EZ line/width are considered efficacy parameters and are presented in the current section. These OCT values will be summarized by treatment group, eye and visit for the Efficacy Evaluable Population using continuous descriptive statistics. OCT data and any comments that may be relevant to the OCT grading will be listed for each subject in the Efficacy Evaluable Population. The measures listed below, regardless of confidence score (high confidence, adequate confidence, inadequate confidence) will be used for summaries and listings.

The following continuous data are considered efficacy endpoints collected as part of the OCT assessments, and are measured in mm:

-A second table with individual observed values and change from baseline over time will also be produced. Subject level listings will also be produced for OCT.

4.8.5. **NIRAF**

The following categorical data are collected as part of the NIRAF assessments performed by an independent reading center according to the schedule of events in Section 2.4 and the Imaging Charter:

- Confidence Score
- Confidence Score Reason

The following continuous data are collected as part of the NIRAF assessments, and summarized using continuous descriptive statistics by treatment group, eye and visit for the Efficacy Evaluable Population:

- Horizontal Diameter of Retained Central Hyperautofluorescent Island (mm)
- Vertical Diameter of Retained Central Hyperautofluorescent Island (mm)
- Area of Retained Central Hyperautofluorescent Island (mm)

Confidence score will be listed and summarized using descriptive statistics for categorical data by treatment group, eye and visit, and confidence score reason will be listed only.

Tables with individual values over time will be produced, for both original and change from baseline values. Subject level listings will also be produced for NIRAF.

4.8.6. **Oculomotor Instability**

A confidence score is collected for each eye as part of the oculomotor instability assessments (with and without fixation) performed by an independent reading center according to the Schedule of Events of

Section 2.4 and the Imaging Charter. For oculomotor instability assessments with and without fixation, confidence score will be listed and summarized using descriptive statistics for categorical data, and comments that may be relevant to the grading will be listed.

The following continuous data are collected as part of the oculomotor instability assessments (with and without fixation), and summarized using continuous descriptive statistics for the Efficacy Evaluable Population:

- Mean Gaze Shift
- Oculomotor Instability
- Overall Oculomotor Instability Measurement
- Excluded Frames Count
- Calculated Frames Count

All measures, regardless of confidence score (high confidence, adequate confidence, inadequate confidence) will be summarized by treatment group, fixation (with or without), eye and visit, and listed. In addition, tables with individual values over time will also be produced, for both original and change from baseline values.

4.8.7. **Pupillary Light Reflex**

PLR imaging measures pupil size with various candela per square meter stimuli (ie, at 4, 40, 400 and 4000 cd/m^2); it is used to test integrity of the sensory and motor functions of the eye. For PLR amplitude parameters, higher values are indicative of better status. For PLR latency parameters, lower values are indicative of better status.

The mean observed value and change from baseline values for the following parameters will be summarized for the different stimuli (ie, at 4, 40, 400 and 4000 cd/m^2) by treatment group, eye and visit for the Efficacy Evaluable Population using descriptive statistics:

- pre-stimulus (mm)

- maximum amplitude (mm)
- 0.9 seconds amplitude (mm)
- Latency (s)

In addition, the following derived parameter will be summarized as well: maximum amplitude minus pre-stimulus at 4000 cd/m^2

Subject level listings will also be produced for PLR.

4.8.8. **VFQ-25/CVAQC**

The observed value and change from baseline values over time for overall VFQ-25 composite scores for adult subjects and CVAQC scores for pediatric subjects will be summarized by treatment group and visit for the Efficacy Evaluable Population and Per Protocol Analysis Set using descriptive statistics. Descriptive summaries of VFQ-25/CVAQC for the subpopulations of subjects defined in Section 4.2.7 will also be provided. Subject level listings will be produced.

- **VFQ-25** Scoring VFQ-25 is a two-step process:

Step 1: original numeric values from the survey are re-coded following the scoring rules outlined in Table 6. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

Step 2: items within each sub-scale are averaged together to create the 12 subscale scores. Table 7 indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

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Composite Score Calculation

To calculate an overall composite score for the VFQ-25, simply average the visiontargeted subscale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each sub-scale, whereas averaging the items would give more weight to scales with more items.

Table 6. Scoring Key: Recoding of Items

Item Numbers	Change original response category(a)	To recoded value of:
1,3,4,15c(b)	1 2 3 4 5	100 75 50 25 0
2	1 2 3 4 5	100 80 60 40 20 0
5,6,7,8,9,10,11,12,13,14,16,16a A3,A4,A5,A6,A7,A8,A9(c)	1 2 3 4 5 6	100 75 50 25 0 *
17,18,19,20,21,22,23,24,25, A11a,A11b,A12,A13	1 2 3 4 5	0 25 50 75 100
A1,A2	0 To 10	0 To 100

(a) Precoded response choices as printed in the questionnaire.

(b) Item 15c has four-response levels, but is expanded to a five-levels using item 15b.

Note: If 15b=1, then 15c should be recoded to "0"

If 15b=2, then 15c should be recoded to missing.

If 15b=3, then 15c should be recoded to missing.

(c) "A" before the item number indicates that this item is an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use all items for a given subscale.

This will greatly enhance the comparability of sub-scale scores across studies.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Table 7. Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	**Number of Items**	**Items to be averaged (after recoding per previous Table)**
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

- **Cardiff Visual Ability Questionnaire for Children (CVAQC)-25**

CVAQC-25 is a visual impairment ability questionnaire for children with 25 items. The response to each item has 5 categories. In this study, the CVAQC-25 total score will be calculated using "Rasch" scoring algorithm. Based on this method, each item has a base measure which calls Item Measure (Table 8), and each category of response has a measure which calls Category Measure (Table 9). To calculate the total score following steps will be taken:

1- For each item, Item Score will be calculated as sum of Item Measure and its Category Measure

2- CVAQC-25 total score will be calculated as average of none missing item scores

Table 8 CVAQC-25: Item Mesaure

Item No.	Item	Item measure
1	Maths Lessons	0.33
2	Science Lessons	-0.25
3	Geography	-0.86
4	Language	0.06
5	Text books/Work sheet	-0.19
6	Smallest print	-2.18
7	Drawing/colouring/ Painting	0.77
8	Mobile phone	0.10
9	Restaurant menus	-0.79
10	Board in your classroom	-0.76
11	Television	1.30
12	Film at the cinema	1.45

Table 9 CVAQC-25: Category Measure

Category measures	
1	-2.96
2	-0.85
3	0.95
4	2.8
5	Missing data

13	Day light	0.42
14	Crowded place	-0.78
15	Public transport	-0.02
16	Bus/Train Time table	-1.90
17	Chat with your friends	1.69
18	Recognising faces	0.70
19	Seeing friend in the Playground	-1.06
20	Use playstation	1.04
21	Computer games	0.49
22	Listening to Music	0.65
23	Swimming	0.76
24	Athletics	-0.15
25	Ball games	-0.81

4.8.9. **Exploratory Endpoints**

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4.9. **Pharmacokinetic Evaluations**

It is expected that the vast majority of measured PK concentrations is below limit of quantification (BLQ). Thus, no pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-24}, AUC_{last} and AUC_{0-inf}) will be derived. All individual measurement results above limit of quantification will be shown in a individual level table, and all measurements – above or below limit of quantification will be presented in the listings on the safety population.

5. CHANGES TO PLANNED ANALYSES

The definition of baseline relevant to PQ-110-001 specified in the protocol has been changed and described in Section 4.2.4 of this SAP.

More precise description with respect to the secondary endpoints are described in Section 2.5.1.2 of this SAP.

The exploratory endpoint “Change in Ellipsoid Zone line by OCT” listed in the protocol which is refer to the same as the secondary endpoint related to OCT has been removed in this SAP. The more detail is described in Section 4.8.4.

The definition of the Efficacy Evaluable Population has been changed from that in specified in the protocol by removing the requirement for at least one post-baseline assessment.

The Pharmacokinetics (PK) Population has been removed since we will not derived pharmacokinetic parameters as it is expected that the vast majority of measured PK concentrations is below limit of quantitation (BLQ).

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7. APPENDIX A

This SAP refers to the following documents:

Sponsor:	ProQR Therapeutics		
Protocol:	PQ-110-002		
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