STATISTICAL ANALYSIS PLAN

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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Statistical Analysis Plan Approval

Prepared by: _____ _____

Reviewed by: _____ _____

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Table of Contents

List of Abbreviations

A	Adult Subject Cohort
AE	Adverse Event
AESI	Adverse Event of Special Interest
ARLNS	Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
BCVA	Best-Corrected Visual Acuity
BRE	Backlit Room Exit®
BRVT	Berkeley Rudimentary Vision Test
C	Concentration
CF	Count Fingers
CL	Serum Clearance or Serum Clearance Level
CME	Cystoid Macular Edema
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
~~CVAQC~~	~~Cardiff Visual Ability Questionnaire for Children (25-items)~~
CS	Clinically Significant
D	Day
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
~~ERG~~	~~Electroretinogram~~
ESR	Erythrocyte Sedimentation Rate
ETDRS	Early Treatment of Diabetic Retinopathy Study
FST	Full-field Stimulus Testing
HCRE	High-Contrast Room Exit®
HCVNC	High-Contrast Visual Navigation Challenge®
HIPAA	Health Information Portability and Accountability Act
HM	Hand Movement
ICH	International Council for Harmonisation
IOP	Intraocular Pressure
ISCEV	International Society for Clinical Electrophysiology of Vision
IVT	Intravitreal
LCA	Leber's Congenital Amaurosis
LCVNC	Low-Contrast Visual Navigation Challenge®
LLOQ	Lower Limit of Quantitation
logMAR	Logarithm of the Minimum Angle of Resolution
LP	Light Perception
M	Month

MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
N	Number of Subjects
n	Number of Observations
N/A	Not Applicable
NCS	Not Clinically Significant
NIRAF	Near-Infrared Autofluorescence
OCI	Oculomotor Instability
SD-OCT	Spectral Domain Optical Coherence Tomography
ONL	Outer Nuclear Layer
P	Pediatric Subject Cohort
p	p-value or probability value
PSC	Posterior Subcapsular Cataract
PDF	Portable Document Format
PK	Pharmacokinetics
PLR	Pupillary Light Reflex
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
$T_{1/2}$	Half-Life
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
V_d	Apparent Volume of Distribution
~~VEP~~	~~Visual Evoked Potential~~
~~VFQ-25~~	~~25-Item Visual Functioning Questionnaire~~
WHO DDE	World Health Organization Drug Dictionary Enhanced
WOCBP	Women of Childbearing Potential

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting ł in support of protocol PQ-110-001, version 6.0 dated 02-Aug-2018.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Council for Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific descriptive statistical methods that will be used.

In addition to this SAP, inferential analyses will be generated by which will also be used to support the CSR. The descriptions of methods and statistical analyses used for these inferential analyses are described separately within the scope of the Cytel SAP of which a copy has been included in whole in and which should be read in conjunction with this SAP.

The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the Clinical Study Report (CSR).Study Objectives

1.1 Primary Objective

The primary objective of the study is to evaluate the safety and tolerability of QR-110 administered via intravitreal (IVT) injection in subjects with Leber's Congenital Amaurosis (LCA) due to the *CEP290* p.Cys998X mutation.

1.2 Secondary Objectives

The secondary objectives of the study are:

- to evaluate the serum pharmacokinetics (PK) 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

1.3 Exploratory Objectives

1.4 Primary Endpoint

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

1.5 Secondary Endpoints

- Frequency and severity of non-ocular Adverse Events (AEs)
- Changes in ophthalmic examination findings
- Change from baseline in Best-Corrected Visual Acuity (BCVA) in treated eye and contralateral eye
- Change from baseline in near-infrared autofluorescence (NIRAF) data in treated eye and contralateral eye:
  - Horizontal diameter
  - Vertical diameter
  - Area
- Changes in SD-OCT findings in treated eye and contralateral eye with horizontal and vertical scan for:
  - Change from baseline in full retinal thickness (FRT) at foveal pit
  - Change from baseline in mean FRT (line scan)
  - Change from baseline in outer nuclear layer (ONL) thickness at foveal pit
  - Change from baseline in extent of ONL region
  - Change from baseline in photoreceptor outer segment thickness (OST) at foveal pit
  - Change from baseline in mean photoreceptor OST (line scan)
- Changes in safety parameters, including vital sign measurements, physical examination findings, electrocardiogram (ECG) and laboratory parameters
- Systemic exposure of QR-110 in serum
- Change from baseline in light sensitivity to red Full-field Stimulus Testing (FST) in treated eye and contralateral eye
- Change from baseline in light sensitivity to blue FST in treated and contralateral eye
- Change from baseline in white Pupillary Light Reflex (PLR) at 4 levels of illumination (ie, 4, 40, 400, and 4000 cd/m^2) in treated eye and contralateral eye:
  - Pre-stimulus
  - Maximum amplitude
  - 0.9 seconds amplitude
- Overall latency (time to react)

1.6 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.

2. Study Design and Procedures

2.1 General Study Design

The first-in-human study of QR-110 will be an open-label, multiple arm, 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 (6 to < 18 years of age) will be determined by the Data Monitoring Committee (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 (e.g., 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 the Screening Visit, subsequently referred to as treatment eye) every 3 months and will be assessed for safety and tolerability at follow-up visits. The worst eye or treatment eye is defined in Section 8.1 of the SAP.

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.

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 is planned but is not within the scope of this SAP.

2.2 Dose Escalation and DMC Review

Specifics of the dose escalation plan are described in detail in Section 4.2.1.5 of the protocol.

Safety review, DMC review and stopping criteria are further detailed in protocol Section 4.2.2 and Section 4.2.4, and the DMC Charter. Otherwise, safety reviews 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.

2.3 Study Cohorts and DMC Review Schedules

QR-110 will be administered at up to 3 escalating dose levels and 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 1). Dose escalation will proceed as described in Section 4.2.1.5 of the protocol. QR-110 will be administered via unilateral IVT injection

in the subject's worse eye (defined in Section 8.1 of the SAP) every 3 months and each subject will receive up to 4 doses of study drug.

While the protocol allows testing of up to 3 dose levels, no dose escalation to the highest dose was performed based on interim study results.

2.4 Study Visits

Study visits will be referred to in all tables and listings as the planned study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule shown in Table 1. Screening assessments may be repeated at a Re-Screening visit to reevaluate eligibility or safety parameters at the Investigator's discretion. In listings the re-screening visit will be "Unscheduled (Day -28 to -1)" and will only be used for further analyses if an average of all pre-dose measures is used for baseline. Dosing visits can occur over multiple days due to time constraints on subjects' schedules and visit procedures. Note that there is no Day 0 and that Day 1 corresponds to the day of first treatment. Any unscheduled visits outside of will be noted as "Unscheduled" on tables and listings. The following table shows the scheduled visits, their planned study day and the acceptable visit windows for each scheduled visit. Scheduled visits that occur outside of the visit window will not be considered unscheduled visits, but will be presented and summarized as the scheduled visit.

2.5 Schedule of Visits and Assessments

3. Study Treatments

In this multiple arm multiple dose escalation study QR-110 will be administered by unilateral IVT injection. Each subject will receive up to 4 doses of QR-110 in their worse eye (defined in Section 8.1 of the SAP) at least 3 months apart and will be assessed for safety and tolerability at follow-up visits. Up to 3 dose levels will be tested (loading dose/maintenance dose):

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

QR-110 Solution for IVT Injection, 10 mg/mL and diluent, will hereby be referred to as IVT injection.
As noted previously in Section 2.3, no subjects were treated at the high dose, therefore only the low dose and mid dose will be considered within the statistical TLFs for this study.

4. Sample Size and Power Considerations

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 Section 4.2.2.2 of the protocol, for a maximum number of subjects up to a total of n = 18.

4.1 Randomization and Masking

No randomization or masking is used for this phase 1b/2 open label safety study.

Evaluators responsible for grading mobility course videos and reviewing and interpreting ophthalmologic imaging (FST, SD-OCT, PLR, OCI, ERG, NIRAF) will be masked to which eye is the treated eye for the entire course of the study to ensure that grading videos and ophthalmologic assessments are unbiased.

4.2 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.

5. Data Preparation

All reported study data will be recorded on the electronic case report forms (eCRFs)

Only the

Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined.

6. Analysis Populations

The analysis population definitions in the SAP will supersede the analysis definitions in the protocol.

6.1 All Enrolled Subjects Population

The All Enrolled Subjects population will consist of all subjects who have provided informed consent, including screen failures as well as subjects who received any QR-110 IVT injection.

6.2 Safety Population

The population for safety analysis will consist of all subjects who received any QR-110 IVT injection.

6.3 Efficacy Evaluable Population

The population for efficacy (clinical activity) analysis will consist of all subjects who received any QR-110 with at least one baseline and one post-baseline efficacy observation or measurement.

6.4 Pharmacokinetic (PK) Population

The population for PK analyses will consist of all subjects who received QR-110 and who have measurable drug concentrations (ie, above the lower limit of quantification) in blood samples.

7. General Statistical Considerations

7.1 Study/Treatment Eye Definition and Unit of Analysis

The study eye will be the treated eye for all efficacy and safety summaries. The study eye will always be referred to as the treated eye on TLFs and is defined as the eye with the worse visual acuity at

Screening. 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 (FST or mobility course score). If the visual function is the same per the Investigator's assessment, then the treated eye will be determined at Investigator discretion.

The unit of analysis for all ocular endpoints will be the eye level. All ocular endpoints will be summarized by eye and by dose group and cohort (ie, adult versus pediatric) for the treated eye and contralateral eye where appropriate. Subject level information, non-ocular AEs, medical history,

7.2 Missing or Inconclusive Data Handling

Other than the imputations described within Section 7.2.1, no special handling of missing data will be made and analyses will be conducted using observed values only.

7.2.1 Missing Mobility Course Composite Score Imputations for Central Reading Center Grading

7.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug in the treated eye for IOP, laboratory parameters, and the safety endpoints slit lamp biomicroscopy, posterior segment/fundus exam, vital signs, and ECG . For ophthalmic parameters BCVA, FST, mobility course, OCI and PLR measured at Screening and Visit 2 (Day 1) the average will be defined as baseline. For other ophthalmic parameters, NIRAF, SD-OCT, and ERG, planned to be done once at baseline, the average will be defined as baseline if the exam is repeated. Change from baseline will be calculated as follow-up visit/time point minus baseline visit/time point.

7.4 Data Analysis Conventions

All data analysis, data summaries, and formal listing preparation will be performed by Statistics & Data Corporation (SDC) for DMC meetings, Interim Analyses and upon the completion of the study. Analyses after the study is completed will be done with a locked database. Statistical programming and analyses will be performed using SAS® version 9.4 or higher. Output will be provided in Rich Text Format (RTF) for tables and Portable Document Format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, sorted by cohort/dose level (in the order of adult cohort 1 [low dose, 160 µg loading dose, followed by up to three 80 µg maintenance doses), pediatric cohort 1 [low dose], adult cohort 2 [middle dose, 320 µg loading dose, followed by up to three 160 µg maintenance doses], and pediatrics cohort 2 [middle dose]), and by eye (OD, OS and OU where applicable) and visit unless otherwise specified. Listings may also include time point, age, and sex where appropriate.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Imaging data will be rounded to 3 decimal places then follow the previously mentioned conventions. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Change from baseline will be calculated as follow-up minus baseline.

All continuous efficacy endpoints will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation, standard error, median, minimum, maximum and 95% confidence intervals (CI) for the mean. Categorical endpoints will be summarized using: number of subjects, frequency, percentages and 95% asymptotic confidence intervals. If data appear highly skewed, natural log or other transformation may be used to compute summary statistics.

Inferential testing is not planned as part of this SAP, summarization will be based on descriptive statistics. Inferential analysis is foreseen within the analyses described within the SAP, further details may be found in the

Unless otherwise specified, summaries will be presented by cohort/dose level for, Adult, and Pediatric separately and for adult and pediatric combined groups of subjects.

7.5 Data Monitoring Committee (DMC)

Safety will be evaluated by the DMC prior to each dose escalation, prior to the first maintenance dose of each cohort, and prior to the enrollment of pediatric subjects by the DMC and Sponsor Medical Monitor. The DMC and Sponsor Medical Monitor will review data on an as needed basis as determined

by the Sponsor and in accordance with the protocol and DMC Charter. As such, a select number of Safety listings are produced for DMC meetings and Sponsor Medical Monitor reviews. The study's reviewing biostatistician will assist the committee members during the open sessions of the meetings in accordance with the DMC Charter.

7.6 Interim Analyses

An interim analysis of all outputs was conducted after the eighth subject in the study had at least 3 months of data in accordance with SAP version 1.0. The interim analysis included all available study data (all monitored and cleaned) at the time of the data snapshot, .

An additional interim analysis (interim analysis 2) of all outputs was performed using all available data (all monitored and cleaned) from all 11 subjects at the time of the data snapshot (ie, after mid-August 2018). SAP Version 1.0 was in effect at the time of this interim analysis.

A third interim analysis, consisting of all outputs produced for interim analysis #2, will be performed once the last subject has completed Visit 15 (end of study visit) and there is a soft lock. This third interim analysis (planned for August 2019) will consist of all outputs for interim analysis 2 and will include all available study data (all monitored and cleaned) at the time of the data snapshot.

No alpha or family-wise error rate adjustments are made for interim analyses at the data for this early phase 1b/2 trial as all analyses are exploratory.

7.7 Adjustments for Multiplicity

No adjustments for multiplicity will be made in this phase 1b/2 study.

8. Disposition of Subjects

Subject disposition will be summarized for the All Enrolled Subjects population. The number and percentage of subjects enrolled will be presented along with the number of subjects who screen fail. The number and percentage of subjects who receive QR-110 will be tabulated by the number of dosed subjects in each QR-110 cohort and dose group.

The number of subjects in each of the analysis populations (Safety and Efficacy) will be displayed by dose group and cohort and percentages will be calculated using all treated subjects as the denominator.

Any change from planned study dosing and maintenance dosing will be displayed on treatment listings by dose group. The subjects who prematurely discontinued from study drug will be summarized by dose group for all treated subjects. An AE listing of subjects who discontinue from study drug will also be presented. Treatment compliance will be displayed in listings and summarized on tables.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized among treated subjects by dose group and cohort for all

subjects. The reasons for study discontinuation that will be summarized include: completed study, withdrawn prior to study drug, administrative reasons, sponsor termination of study, adverse event(s), protocol deviation(s), and other. A subject listing will be provided that includes the date of and reason for study discontinuation.

The number and percentage of subjects with major protocol deviations will be summarized among treated subjects by dose group. Major protocol deviations will be further summarized by category (e.g., visit conducted out of window) for all categories with one or more major protocol deviation. The protocol deviation categories include: informed consent, inclusion/exclusion, enrollment, subject was NOT treated with assigned treatment, assessment / procedure NOT conducted per protocol requirements, missed visit, visit conducted out of window, assessment not done, site failure to report AE/SAE, subject non-compliance and other. Protocol deviations related to inclusion/exclusion violations will have the specific criterion number indicated within the subject data listing. A subject listing will be provided that includes the date of the deviation, the deviation description and the classification of whether the deviation was judged to be major or minor.

In addition, subject listings will be provided that include informed consent date and inclusion and exclusion criteria violations.

9. Demographics

The demographic variables collected in this study include age, sex, childbearing potential, acceptable method of birth control, race and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Demographic variables will be summarized for the Safety Population, separately by dose group and cohort (Adult, Pediatric, and Combined).

Collection of date of birth depends on local regulations at study sites. In cases where only the year of birth is allowed to be collected, the month and day will be recorded in the eCRF as July 1 with the appropriate year.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: 6 years to <18 years, 18 years to <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (informed consent date – date of birth) / 365.25 truncated as an integer

The number and percentage of subjects will be presented, overall and by treatment, for age category, gender, race and ethnicity.

A subject listing that includes all demographic variables will be provided for each dose group.

9.1 Genotyping

Genotyping will be assessed by any historical records of the disease or new genetic testing for inclusion in the study. Date of the test, and any genetic mutation will appear on subject level listings.

9.2 Baseline Characteristics

A summary listing of baseline characteristics will be produced showing select demographic, ocular history, disease history (including date of diagnosis and age at diagnosis), visual acuity, and other ocular information.

10. Medical History and Concomitant Medications

10.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Non-ocular medical history will be summarized using discrete summary statistics and presented by dose group at the subject (i.e., counts and percentages based on incidence of subjects with an event) and event level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. Ocular medical history will be similarly summarized at the subject level (i.e., incidence of subjects with an event) and event level, separately for the treated eye and contralateral eye. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

Listings of medical history will be generated separately for ocular and non-ocular data.

10.2 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (Enhanced B2, March 2017) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins) then the drug name will be summarized as the preferred name. Any un-coded terms will be summarized under the ATC classification and preferred name of “Encoded.”

Concomitant medications are defined as those medications listed as having been taken 1) prior to initiation of study drug administration and continuing for any period following the first administration of study drug or 2) at any time following the first administration of study drug or 3) any pre-medication taken in conjunction with the normal conduct of the study (e.g., and medications for pupil dilation and/or general sedation/anesthesia for the IVT injection of the study drug).

Non-ocular and ocular concomitant medications will be summarized separately using the Safety population. Medications will be tabulated for each dose group using frequencies and percentages, ocular medications will be further summarized separately for treated eye and contralateral eye. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each dose group. Listings of concomitant medications will be generated separately for ocular and non-ocular data.

11. Treatment Exposure

All doses are observed and administered by study staff. Therefore, treatment compliance will not be calculated. Treatment exposure will be assessed by calculating the number of doses expected, number of actual doses received, cumulative dosage (µg), and the duration of exposure. Number of doses expected will be determined by the highest visit completed, as follows:

- Study discontinuation after Visit 2 but before Visit 9 (Month 3) implies 1 dose was expected.
- Study discontinuation after Visit 9 but before Visit 13 (Month 6) implies 2 doses were expected.
- Study discontinuation after Visit 13 but before Visit 18 (Month 9) implies 3 doses were expected.
- Study discontinuation after Visit 18, or completion of study, implies 4 doses were expected.

Number of actual doses received will be summarized as both continuous and categorical outcome (i.e., 1, 2, 3, or 4 doses received). Duration of exposure will be calculated in days as the date of last dose – the date of first dose + 1. Treatment exposure parameters will be summarized descriptively by dose group and cohort.

12. Safety and Tolerability Analyses

12.1 Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable, noxious and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with use of a study drug or other protocol-imposed intervention, regardless of attribution. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period ends 90 days following the last administration of study drug or the subject's EOS visit, whichever is later. 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. All AEs will be coded using the MedDRA 20.0.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that study treatment is initiated. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

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 (non-TEAE).

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by dose group. This summary will also include breakdowns of TEAEs further categorized as ocular (treated eye and contralateral eye separately) or non-ocular, serious TEAEs (SAEs), TEAEs by maximum severity, TEAEs by maximum relationship, and TEAEs leading to subject withdrawal.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC) and preferred term (PT). Non-ocular TEAEs will be summarized using discrete summary statistics and presented by dose group at the subject and event level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level for study and contralateral eyes separately. If the same PT is reported for a subject multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if multiple conditions within the same SOC are reported, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC. The occurrence of non-ocular and ocular TEAEs will also be tabulated by SOC and PT for the following: maximal severity and suspected relationship to study drug.

Separate summaries will be provided for the following categories of AEs:

- All AEs
- Ocular TEAEs in the treated eye and contralateral eye (includes treatment-related events)
- Non-ocular TEAEs (includes treatment-related events)
- TEAEs leading to treatment discontinuation
- TEAEs leading to subject withdrawal or treatment discontinuation
- Serious TEAEs (SAEs)
- TEAEs by maximum severity
- TEAEs by maximum relationship
- TEAEs of special Interest

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made

irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *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.

Summaries of TEAEs by maximal severity will be presented for ocular AEs and non-ocular AEs separately. The number of subjects with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by dose group. To count the number of subjects with any TEAEs, if a subject has multiple TEAEs coded to the same PT within the same SOC, the subject will be counted once under the maximal severity.

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, the Investigators were instructed to apply the following general guideline:

- *Not Related:* The AE has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after 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 (i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that 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.

All TEAEs will be presented in a subject listing. The TEAEs leading to study treatment discontinuation will be listed separately. In addition, all serious AEs will be presented in a separate listing.

12.1.1 Adverse Events of Special Interest (AESI)

12.2 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination of the cornea, conjunctiva (palpebral and bulbar), anterior chamber including flare, iris, lens including nuclear, cortical and posterior subcapsular cataract opacity scores, and eyelid/lashes will be performed according to the ocular exam detailed in Section 3.5 of the SAP. The results will be graded as normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS) with flare scores ranging from 0 to 4+ in whole number increments and lens opacity scores ranging from <1 to >3 in half-point increments.

The results will be summarized using counts and percentages for each dose group and for all subjects for each eye (treated eye and contralateral eye). Tables with percentages will be based on the number of subjects in each dose group with responses. A subject listing of the slit-lamp biomicroscopy parameters will also be produced including the AESIs related to anterior chamber flare and lens opacities.

12.2.1 Anterior Chamber Flare

Anterior chamber flare will be graded according to the SUN Working Group Grading Scheme using a 5-unit scale where 0 = None, 1+ = Faint, 2+ = Moderate (iris and lens details clear), 3+ = Marked (iris and lens details hazy) and 4+ = Intense (fibrin or plastic aqueous). Anterior chamber flare grade at each visit and change from baseline will be tabulated using continuous and discrete summary statistics.

AESI related to anterior chamber flare will include those TEAEs with MedDRA PT of ‘Flare’, as described in . The onset date of each reported AESI will be compared to dates of slit lamp biomicroscopy results, and exams with dates between the onset date and resolution of the corresponding AESI will be flagged as having led to an AESI report. The incidence of AESI related to lens opacities will be included in the aforementioned discrete summary by visit.

AESIs related to anterior chamber flare will also be summarized with counts and percentages for each dose group and cohort with the definition of the anterior chamber flare related AESI according to Section 13.1.1 of the SAP. AESI related to anterior chamber flare will include those TEAEs with MedDRA PT of ‘flare’. In order to establish if results at individual visits resulted in an AESI report or not, the onset date of each reported AESI related to anterior chamber flare will be compared to dates of slit lamp biomicroscopy results, and exams with dates between the onset date and resolution of the corresponding AESI will be flagged as having led to an AESI report.

12.2.2 Lens Opacity Examination

Clinical lens opacities will be graded using the Age-Related Eye Diseases Study (AREDS) protocol and the Clinical Lens Grading System (ARLNS) on a 7-unit scale from <1 to >3 with half unit increments. . Lens nuclear opacity, cortical opacity and PSC opacity and changes from baseline summarized using continuous and discrete descriptive statistics.

AESIs related to lens opacities will also be summarized with counts and percentages for each dose group and cohort with the definition of the lens opacity related AESI according to Section 13.1.1 of the SAP. AESI related to lens opacities will include those TEAEs with MedDRA PT of 'eye opacity'. In order to establish if results at individual visits resulted in an AESI report or not, the onset date of each reported AESI related to lens opacities will be compared to dates of slit lamp biomicroscopy results, and exams with dates between the onset date and resolution of the corresponding AESI will be flagged as having led to an AESI report.

12.3 Posterior Segment/Fundus Examination

A posterior segment/fundus examination of the vitreous, macula, optic nerve, peripheral retina and choroid will be performed at each visit. The results will be graded as normal, abnormal NCS or abnormal CS. Vitreous haze is also assessed with possible scores of 0, 0.5+, 1+, 2+, 3+, or 4+. Cup-to-Disc ratio is also assessed in the Posterior Segment/Fundus Examination on a 0.1 to 1.0 scale in increasing increments of 0.1.

The results will be summarized using counts and percentages for each dose group and for all subjects at each visit for each eye (treated eye and contralateral eye). Percentages will be based on the number of subjects in each dose group with responses. AESI will also be summarized with counts and percentages for each dose group and cohort with the definition of the vitreous haze related AESIs according to Section 12.1.1 of the SAP. A subject listing of the posterior segment/fundus examination parameters will also be produced. Vitreous haze related AESI will include those TEAEs with MedDRA PT of 'vitreous haze'. In order to establish if results at individual visits resulted in an AESI report or not, the onset date of each reported AESI related to lens opacities will be compared to dates of fundus exam results, and exams with dates between the onset date and resolution of the corresponding AESI will be flagged as having led to an AESI report.

12.4 Intraocular Pressure (IOP)

Intraocular pressure (IOP) will be assessed by tonometry (Goldmann Applanation Tonometer, Tono-pen, Noncontact Tonometer [puff tonometry], or Icare Tonometer [rebound tonometry]) according to the optical exam schedule of Section 3.5 of the SAP. Results will be taken from a single measurement per eye and will be recorded in mmHg.

The IOP values and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics by visit and eye for each dose group and for all subjects. Baseline IOP is the last measurement prior to the first dose of study drug in the treated eye and may occur on a different date than dosing. The first measure taken immediately post-dose will be included in a change from baseline analysis. A subject listing of IOP will also be produced include IOP related AESIs. Tables will also include AESI for each visit with counts and percentages for each dose

group and cohort with the definition for the IOP related AESI according to Section 13.1.1 of the SAP. IOP related AESI will include those TEAEs with MedDRA PT of 'intraocular pressure increased'. In order to establish if results at individual visits resulted in an AESI report or not, the onset date of each reported AESI related to IOP will be compared to dates of IOP assessments, and assessments with dates between the onset date and resolution of the corresponding AESI will be flagged as having led to an AESI report.

12.5 Physical Examination

The physical examination results, graded as normal or abnormal NCS or abnormal CS, will be summarized by dose group and for all subjects using counts and percentages (including a summary of baseline values). A subject listing of the physical examination results will also be produced.

12.6 Vital Signs

Vital signs, including pulse, blood pressure, height, weight and temperature, will be summarized with continuous descriptive statistics at each day (including a summary of baseline values) by dose group and for all subjects. Change from baseline will also be summarized to each post-baseline visit. A subject listing of the vital signs results will also be produced.

12.7 Electrocardiogram (ECG)

Heart rate (HR), PR, QRS, QT, and QTc with correction specified as either Bazett or Fridericia, intervals will be summarized using descriptive statistics by dose group and for all subjects at each visit the assessment is taken. Change from baseline to each post-baseline visit and time point will be also summarized. A subject listing of the ECG results will also be produced.

12.8 Clinical Laboratory Data

Clinical laboratory data including hematology, coagulation, serum chemistry and urinalysis are collected at specified visits. Other lab tests which are collected and will be summarized include Complement C4 NEPH, C-reactive protein (CRP), complement total, and erythrocyte sedimentation rate. The quantitative variables will be summarized by dose group and for all subjects with continuous descriptive statistics at each visit and time point where appropriate. The qualitative variables (counts and percentages) will be summarized by dose group and for all subjects at each visit and time point where appropriate. Change from baseline will also be summarized by dose group and for all subjects.

13. Pharmacokinetic Analyses

Pharmacokinetic (PK) analyses will be primarily performed on the PK population with observed data only. 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 level will be estimated using the formula: $CL = Dose/AUC_{0-\infty}$.
- V_d (if measurable serum levels are obtained and an elimination rate constant (λz) 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 to one half of LLOQ.

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

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

Drug concentrations will be summarized by nominal time point if 3 or more values are available.

Descriptive statistics for PK parameters will be performed if ≥50% of subjects have evaluable data and number of values to summarize is ≥3.

Geometric means and coefficients of variation will be tabulated for C_{max}, C_0, $AUC_{0-tlast}$, $AUC_{0-\infty}$, CL, and V_d for each dose group if possible. Tmax will be summarized by median, minimum and maximum. Mean, standard deviation, minimum and maximum will be provided for $T_{1/2}$.

14. Efficacy Analyses

The Efficacy Evaluable population will be used for the efficacy analyses including mobility course, BCVA, FST, OCI, PLR and ~~VFQ-25/CVAQC~~. Ocular imaging endpoints will also be summarized with the Efficacy population for all imaging endpoints including ERG imaging, SD-OCT (Photoreceptor Outer Segment Thickness, Full Retinal Thickness, ONL Thickness, Macular Edema), and NIRAF imaging. Selected efficacy endpoints which also constitute a safety outcome may be rerun using the Safety Population if the Efficacy Evaluable and Safety Populations differ. Tables will summarize endpoints using continuous or categorical descriptive statistics by visit and time point where appropriate. Change from baseline visit will be calculated as follow-up visit minus baseline visit. Tables will include sections for adults, pediatrics and combined cohorts according to dose groups.

Subject listings by visit, time point (when applicable) and eye will also be produced.

14.1 Visual Acuity (BCVA) with ETDRS and BVRT

The logarithm of the minimum angle of resolution (logMAR) visual acuity is assessed using an EDTRS chart according to Section 3.5 of this SAP. Light perception (LP), detection of hand movement (HM) and ability to count fingers (CF) are also acceptable measures of visual acuity for this study. The Berkeley Rudimentary Vision Test (BRVT) will also be used to assess subjects' visual acuity. Since BCVA is an efficacy endpoint but also a safety output, this analysis will be produced primarily for the Efficacy Evaluable Population, and only repeated for the Safety Population if the Safety Population is different than the Efficacy Evaluable Population.

The observed value and change from baseline visual acuity will be summarized for each eye (treated eye and contralateral eye) for BCVA using continuous descriptive statistics on the logMAR scale by visit for each dose group and for all subjects. If there is no logMAR evaluation available from the EDTRS chart or BRVT assessment, visual acuity measures of LP, HM, and CF will be summarized using the following logMAR equivalents (refer to Section 21 Appendix 1 for full table):

- Light Perception = 4.0 logMAR
- Hand Movement = 3.0 logMAR
- Count Fingers = 2.0 logMAR

BRVT will be summarized in a similar manner as described for BCVA via ETDRS, with discrete summary statistics for frequency of Light Perception, Black White Discrimination, White Field Projection, and Cord Pair. The BRVT logMAR value will be summarized with continuous descriptive statistics. For BRVT, if the Light Perception question is not answered on the eCRF, then values will be imputed from the corresponding Best Corrected Visual Acuity (BCVA) Light Perception answer.

BCVA related AEs of special interest (AESI) will also be summarized with counts and percentages for each dose group and cohort with the definition of the BCVA related AESI according to Section 13.1.1 of the SAP. BCVA related AESI will include those TEAEs with MedDRA PTs of 'visual acuity reduced' or 'blindness'. In order to establish if results at individual visits resulted in an AESI report or not, the onset date of each reported AESI related to BCVA will be compared to dates of BCVA assessments, and assessments with dates between the onset date and resolution of the corresponding AESI will be flagged as having led to an AESI report.

A subject listing of visual acuity will also be produced. This BCVA listing will include a variable that indicates if a subject had a visual acuity change from baseline of ≥0.3 (15-letters or more) on the logMAR scale.

Shifts from baseline to post-BL in vision category will be summarized for BCVA using categories of LP, HM, CF and logMAR BCVA (i.e. visual acuity reported as better than CF), and for BRVT using categories of light perception, black white field discrimination, white field projection and logMAR BRVT (i.e. visual acuity better than light perception).

14.2 Red, Blue and White Full-Field Stimulus Testing (FST)

The Full-Field Stimulus Testing (FST) captures threshold measurements for each stimulus (red, blue and white light) that will be evaluated. Measurements with a Fail value of "0" are successful. A measurement with a Fail value of "1" is unsuccessful. If the threshold value fails, the next successful value will be captured. FST thresholds will be measured according to the imaging schedule of Section 3.5 of the SAP and Imaging Charter.

The FST values (ie, light sensitivity) and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics and 95% CIs by visit and eye for each dose group and stimuli color for all subjects. Baseline FST is the average of all pre-dose FST assessments for that stimuli. Post-Baseline FST values are the average of all FST values for the given eye at a given time point and light color. An analysis of all failed and successful thresholds will be produced as well as an analysis of only successful thresholds. A subject listing of all failed and successful threshold FST will also be produced.

14.3 Pupillary Light Reflex (PLR)

Pupillary Light Reflex (PLR) imaging will measure the pupil size in various candela per square meter stimulus (ie, at 4, 40, 400 and 4000 cd/m^2). Maximum amplitude, delayed amplitude at 0.9 sec and overall latency (time to react) will be measured according to the imaging schedule of Section 3.5 of the SAP and Imaging Charter.

The PLR values and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics and 95% CIs by visit and eye for each dose group and for all subjects. Baseline PLR is the average of all pre-dose PLR assessments. A subject listing of PLR will also be produced.

14.4 Oculomotor Instability (OCI)

Oculomotor Instability (OCI) will be measured with fixation and without fixation according to the imaging schedule of Section 3.5 of the SAP and Imaging Charter. The OCI values and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics and 95% CIs by visit and eye for each dose group for all subjects. Baseline OCI is the average of all pre-dose OCI assessments. A subject listing of OCI will also be produced.

14.5 Electroretinogram (ERG) in Scotopic and Photopic Conditions

Electroretinogram (ERG) will measure a-wave (initial corneal-negative deflection) and b-wave (corneal-positive deflection) under scotopic (low light conditions or dark adaptive measures) and photopic (normal light conditions or light adaptive measures) conditions. Dark adaptive oscillatory potentials, light adaptive flicker response, overall rod and cone waves and overall rod and cone functioning will also be assessed. ERG measurements will be taken in accordance to the imaging schedule of Section 3.5 of the SAP and the Imaging Charter.

The ERG values and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics and 95% CIs by light/dark adaptive condition, visit and eye for each dose group for all subjects. Baseline ERG is the average of all pre-dose ERG assessments for that light/dark adaptive condition. A subject listing of ERG will also be produced.

14.6 Spectral Domain Ocular Coherence Tomography (SD-OCT)

Spectral Domain Ocular Coherence Tomography (SD-OCT) will measure Full Retinal Thickness (FRT), Outer Nuclear Layer (ONL) Thickness, presence of Macular Edema, and Photoreceptor Outer Segment Layer Thickness (PROST) according to the imaging schedule of Section 3.5 of the SAP and the Imaging Charter.

Since SD-OCT is an efficacy endpoint but also a safety endpoint, this analysis will be produced primarily for the Efficacy Evaluable Population, and repeated for the Safety Population only if the Safety Population is different than the Efficacy Evaluable Population.

The SD-OCT values and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics and 95% CIs by visit and eye for each dose group for all subjects. All measures, regardless of confidence score will be used for analyses. Baseline SD-OCT is the average of all pre-dose SD-OCT assessments if the exam was repeated. Tables will include

AESI for each visit with counts and percentages for each dose group and cohort with SD-OCT AESI according to Section 13.1.1 of the SAP. Post-BL values for individual SD-OCT parameters which are considered to have met AESI criteria will be based on determinations provided by the imaging reader.

A subject listing of SD-OCT will also be produced including an overview of SD-OCT related AESIs if reported.

14.7 Near-Infrared Auto Fluorescence (NIRAF)

Near-Infrared Auto Fluorescence (NIRAF) will measure the retained central hyper-autofluorescent island in subjects' eyes with the horizontal and vertical diameters and the overall area according to the imaging schedule of Section 3.5 of the SAP and Imaging Charter.

Since NIRAF parameters are an efficacy outcome but also represent a safety outcome, this analysis will be produced primarily for the Efficacy Evaluable Population, and repeated for the Safety Population only if the Safety Population is different than the Efficacy Evaluable Population.

The NIRAF values and changes from baseline for each eye (treated eye and contralateral eye) will be summarized using continuous descriptive statistics and 95% CIs by visit and eye for each dose group for all subjects. Baseline NIRAF is the average of all pre-dose NIRAF assessments if the exam was repeated. All measures, regardless of confidence score will be used for analyses. Tables will include NIRAF related AESIs for each visit with counts and percentages for each dose group and cohort with definition of the NIRAF related AESI according to Section 13.1.1 of the SAP. Post-BL values for individual NIRAF parameters (e.g, horizontal diameter decreased, vertical diameter increased) which are considered to have met AESI criteria will be based on determinations provided by the imaging reader.

A subject listing of NIRAF will also be produced including footnotes and superscript markers for each AESI.

15. Changes from Protocol-Stated Analyses

15.1 Analysis Populations

Safety Population

The safety population in Protocol Section 10.3 is defined as all subjects who receive any QR-110 or pre-medications required for the study. “Or pre-medications” is removed from the safety population so analyses will only contain subjects who receive the active study IVT injection.

Per Protocol Efficacy Population

The per protocol efficacy population is defined in Protocol Section 10.3, however due to the limited number of potential subjects for such a population, additional analyses on a Per Protocol population will not be conducted.

15.2 Data Analysis Conventions - Baseline

In Sections 8.12, 10.4 and in the Study Plan section of the synopsis in the protocol, baseline is referred to as the highest level of visual functioning in the case of repeat assessments, the measure reflecting the highest level of visual function will be used as baseline. Contrary to this, baseline will be measurement specific according to the current SAP Section 8.3.

16. References

17. Revision History

17.1 Revision 01

. Changes were made throughout the SAP for the following reasons:

- To align to the information found within the current version (6.0) of the protocol.
- To update the description of the analysis methods to incorporate decisions made during previous interim analysis as well as to better harmonize the SAP text to the actual outputs which have been produced.
- To add details relevant to generation of new or revised tables and listings which will be produced for final analysis, following end of study database lock.

The following table summarizes major revisions which implemented with this version.

Summary of Changes in the Statistical Analysis Plan

Section Number	Description of Change	Rationale
1	Added brief description of additional SAP prepared by ~~Cytel, Inc.~~ for analyses produced beyond scope of this SAP.	Comprehensive accounting of planned analyses.
2.5	Additional details for protocol defined list of endpoints were added	To enhance clarity
3.3	Update enrollment status, including no dosing at high dose	Clarify dose groups for analysis
7	Added All Enrolled Subjects Population,	Needed for analysis.
8.2 and 8.2.1		
8.3	Added “and most safety endpoints.”	Assumption was clarified.
8.4	The “combined” cohort is 1st.	Re-organized cohort order to match with actual output.
8.5	Added “prior to the first maintenance dose of each cohort,”.	Added information to rational for DMC meetings based on Sponsor’s rational.
8.6	Second and third interim analysis paragraph added.	Added for additional interim analysis to explain rational.
10.2	Added section to explain baseline characteristics overview listing.	Added for Sponsor request analyses.
11	Ocular summaries to be produced separately for TE and CE	Sponsor requested analysis.

12	Added variable “number of doses received” and added derivation of “number of doses expected”	Sponsor requested analysis, and to provide clarification of how expected doses is derived.
13.1.1	Updated description of identification of AESI events	Updated description to match current process.
13.2-13,4	Updated description identification of specific AESI and for linking of AESI within AE data to individual examination	Updated description to match current process.
15	Updated description of analysis populations to be used for efficacy analyses. Added “responder analysis” section and tables.	Safety Population to be used only if differs from Efficacy Evaluable. Added for Sponsor request analyses.
15.1	Visual Acuity moved from Safety Section (formerly 13.2) to Efficacy Section (15.1) Updated description of AESI identification for BCVA. Added shift table for BCVA and BRVT.	BCVA is primary efficacy endpoint for analysis. To align to current process. Table was being produced, description had been omitted from SAP text.
15.6, 15.7	Added conditional rerun of results on Safety Population. Updated description identification of specific AESI and for linking of AESI within AE data to individual examination	Sponsor requested analysis. Updated description to match current process.
15.8.1	Mobility course section updated to provide additional details of testing procedure, including courses used.	To provide greater clarity of mobility course assessment.
17 and 17.1	Revision History section added	Revision History section added

21. Appendices

21.1 Appendix 1: Table of Equivalency – Visual Acuity

Visual Acuity	Snellen Notation	Decimal Fraction = Monoyer Scale	LogMAR = ETDRS Notation = Study Notation	Equivalence BRVT test	
Light Perception					
Visual Acuity at 60 cm = 2 feet				**Visual Acuity at 1 m**	**Visual Acuity at 25 cm**
Hand motion[10]	20/20000	0.001	+3.00		
	20/16000	0.00125	+2.9		GA 200M
			+2.7		GA 125M
	20/8000	0.0025	+2.6		STE 100M
			+2.5		GA 80M
			+2.4		STE 63M
	20/4000	0.005	+2.3		GA 50M
			+2.2		STE 40M
Counting Fingers[10]	20/2000	0.010	+2.00	STE 100M	STE 25M
	20/1600	0.0125	+1.9		
	20/1200	0.016	+1.8	STE 63M	
	20/1000	0.020	+1.7		
Visual acuity at 1m	20/800	0.025	+1.6	STE 40M	
	20/600	0.033	+1.5		
	20/500	0.04	+1.4	STE 25M	
	20/400	0.05	+1.3		
	20/320	0.063	+1.2		
	20/250	0.08	+1.1		
Visual Acuity at 4 m	20/200	0.10	+1.00		
	20/160	0.125	+0.9		
	20/125	0.16	+0.8		
	20/100	0.20	+0.7		
	20/80	0.25	+0.6		
	20/63	0.32	+0.5		
	20/50	0.40	+0.4		
	20/40	0.50	+0.3		
	20/32	0.63	+0.2		
	20/25	0.80	+0.1		
	20/20	1	0		
	20/16	1.25	-0.1		
	20/12.5	1.6	-0.2		
	20/10	2	-0.3		

References: Bailey 1976; Bainbridge 2008; Ferris 1982; Ghazi 2016; Holladay 1997; Holladay 2004; Lange 2009; Maguire 2008; Schulze-Bonsel 2006; Simonelli 2010; Sloan 1951