STATISTICAL ANALYSIS PLAN

A Multiple-Site, Phase 1/2, Safety and Efficacy Trial of a Recombinant Adeno-associated Virus Vector Expressing Retinoschisin (rAAV2tYF-CB-hRS1) in Patients with X-linked Retinoschisis

Sponsor: Applied Genetic Technologies Corporation (AGTC)

Protocol Number: AGTC-RS1-001

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List of Abbreviations

AAV	Adeno-Associated Virus
AE	Adverse Event
AGTC	Applied Genetic Technologies Corporation
ANOVA	Analysis of Variance
BCEA	Bivariate Contour Ellipse Area
BCVA	Best-Corrected Visual Acuity
CAI	Carbonic Anhydrase Inhibitor(s)
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic Case Report Form
ERG	Electroretinography or Electroretinogram
ETDRS	Early Treatment of Diabetic Retinopathy Study
ffERG	Full-field Electroretinogram
FVQ_CYP	Functional Vision Questionnaire for Children and Young People
HOV	Hill of Vision
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
logMAR	Logarithm of the Minimum Angle of Resolution
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	Multifocal Electroretinogram
MNREAD	University of Minnesota trademark for low vision visual acuity charts
MTD	Maximum Tolerated Dose
OCT	Optical Coherence Tomography
PCR	Polymerase Chain Reaction
PDF	Portable Document Format
PT	Preferred Term
rAAV	Recombinant adeno-associated virus
rAAV2tYF-CB-hRS1	Recombinant adeno-associated virus vector expressing retinoschisin
RS1	Retinoschisin (protein or gene)
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SD-OCT	Spectral Domain - Optical Coherence Tomography
SKP	Semi-automated Kinetic Perimetry
SOC	System Organ Class
VA	Visual Acuity
VFQ-25	25-question Visual Function Questionnaire

XLRS	X-linked Retinoschisis

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol AGTC-RS1-001, Version 6.0 dated 18 July 2017.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (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 statistical methods that will be used. 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.

2. Study Objectives

The primary objective is to evaluate the safety of recombinant adeno-associated virus vector expressing retinoschisin (rAAV2tYF-CB-hRS1) in patients with X-linked retinoschisis (XLRS). The secondary objective is to evaluate the efficacy of rAAV2tYF-CB-hRS1 in patients with XLRS.

3. Study Variables

3.1 Primary Variable

The primary variables are the:

- Number and proportion of participants experiencing ocular or non-ocular adverse events (AEs),
- Number and proportion of participants experiencing any clinically significant abnormal hematology or chemistry parameter

3.2 Secondary Variables

The secondary variables are change over time in:

- Best corrected visual acuity (BCVA),
- Schisis detected by optical coherence tomography (OCT) with infrared montage, to include volumetric analysis of schisis cavity size,
- Static and kinetic visual fields measured using the Octopus perimeter,
- Visual fields measured by microperimetry,
- Reading speed test,
- Contrast sensitivity,
- Full-field electroretinogram (ffERG),

- Multifocal electroretinogram (mfERG), and
- Quality of life questionnaire responses.

3.3 Other Outcome Variables

Other outcome variables include the following:

- Change over time in fundus photographs,
- Change over time in titers of serum antibodies or IFN-γ ELISPOT responses to retinoschisin (RS1).
- Change over time in serum antibodies and IFN-γ ELISPOT responses to AAV, and
- The number and proportion of participants with rAAV2tYF-CB-hRS1 vector DNA detectable in blood by polymerase chain reaction (PCR) assay.

4. Study Design and Procedures

4.1 General Study Design

This is a non-randomized, open-label, Phase 1/2 dose escalation study of the safety and efficacy of rAAV2tYF-CB-hRS1 administered by intravitreal injection in one eye in individuals with XLRS. The primary objective is to evaluate safety and the secondary objective is to evaluate efficacy.

Each participant is to receive rAAV2tYF-CB-hRS1 by intravitreal injection in one eye on a single occasion as outlined in the schematic below.

Schematic of Study Design:

Group [a]	Age (yr)	Number of Subjects	Dose Level		
			vg/mL	Volume	vg per eye
1A	≥ 18	3	1.43×10^{12}	0.07 mL	1×10^{11}
1B	≥ 18	3	1.43×10^{12}	0.07 mL	1×10^{11}
2	≥ 18	3	4.3×10^{12}	0.07 mL	3×10^{11}
2A	6-17	Up to 6	4.3×10^{12}	0.07 mL	3×10^{11}
3	≥ 18	3	4.3×10^{12}	0.14 mL	6×10^{11}
4	≥ 6	Up to 15	MTD [b]	MTD	MTD

[a] Visual acuity not better than 58 Early Treatment Diabetic Retinopathy Study (ETDRS) letter score in Group 1A, 63 in Groups 1B, 2, 2A & 3, 68 in Group 4.
[b] MTD = maximum tolerated dose determined in Groups 1A, 1B, 2 and 3 for adults, in Groups 1A, 1B, 2, and 3 (adult participants only) and 2A (pediatric participants only) for pediatric participants.

Participants in Groups 1A, 1B, 2 and 3 are at least 18 years of age and receive the vector at a lower dose (Groups 1A and 1B), middle dose (Group 2) or higher dose (Group 3). Participants in Group 1A have visual acuity that is worse than participants in subsequent groups (ETDRS letter score of 58 in Group 1A and 68 in other groups). Participants in Group 2A will be 6-17 years of age and receive the

vector at the middle dose level. Participants in Group 4 will be at least 6 years of age and will receive the vector at the maximum tolerated dose (MTD) determined in Groups 1A, 1B, 2, and 3 for adults; in Groups 1A, 1B, 2, and 3 (adult participants only) and 2A (pediatric participants only) for pediatric participants.

Participants in all groups are selected from individuals who are not being treated with a carbonic anhydrase inhibitor during the study and have not been treated with any carbonic anhydrase inhibitor within the 3 months prior to enrollment in the study. Participants are asked not to begin treatment with a carbonic anhydrase inhibitor within 6 months after study agent administration.

Individuals who have participated in the natural history study XLRS-001, entitled “Clinical Evaluation of Individuals with XLRS”, may have discontinued their participation in that study and enrolled in this study if all appropriate entry criteria were met. In this case, results of the evaluations from the most recent visit in the natural history study could be used as part of the appropriate screening visit evaluations for this study, as long as all the evaluations were conducted according to the Study Manual of Procedures and Reading Center Manual of Procedures of this study, and the visit occurred no more than 3 months prior to the planned date of study agent administration. If the most recent visit occurred more than 3 months prior to the planned date of study agent administration, all screening visit examinations are performed.

Enrollment began with Group 1A and will proceed to subsequent groups after review of safety data by a Data and Safety Monitoring Committee (DSMC). After review of safety data from Group 1A, participants will be enrolled in Groups 1B and 2 concurrently. After review of safety data from Groups 1A, 1B and 2, participants will be enrolled in Group 3. After review of safety data from Groups 1A, 1B, 2, and 3, participants ≥18 years of age will be enrolled in Group 4. As ocular inflammation has been seen in the first 12 subjects enrolled in the study and pediatric participants might be more prone to inflammation, pediatric participants (age 6-17) in this study will first be treated at the middle dose (Group 2A) prior to the enrollment in Group 4.

Within groups 1A, 2, 2A and 3, enrollment of participants will be staggered by at least 2 weeks to allow adequate time for review of safety information by the investigators and sponsor.

Within group 4, enrollment of the first 3 pediatric participants will be staggered by at least 2 weeks to allow adequate time for review of safety information by the investigators and sponsor.

Approximately 27 participants are to be enrolled in this study. Enrollment in this study is anticipated to take approximately 30 months. Enrolled participants will have frequent follow-up visits during the first year after study agent administration.

To monitor for delayed AEs and assess the duration of any changes in visual function or structure that occur, participants are followed annually for an additional 4 years after the Month 12 visit.

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

Time relative to study agent administration	Screen[a]	BL[b]	Day				Month						Year	ET[d]
			0	1	7	14	1	2	3	6	9	12	2-5[c]	
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13-16**	
Informed consent/assent	✓													
Inclusion/exclusion criteria	✓	✓												
Initial medical history	✓													
Blood for DNA testing[e]	✓													
Physical exam[f]	✓													
Safety labs[f,g]	✓				✓	✓								✓*
Coagulation (PT and PTT)[f]	✓													
Blood for AAV antibodies	✓						✓		✓	✓		✓	✓	✓
Blood for RS1 antibodies		✓					✓		✓			✓	✓	✓
Blood for PBMC		✓					✓	✓	✓					✓*
Blood for vector DNA		✓		✓	✓	✓								✓*
Prophylaxis for inflammation		✓												
Study Agent Administration			✓											
Clinical Evaluation[h]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Review		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ophthalmic Examinations[i]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Visual Acuity	✓	×2		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Octopus visual fields	✓	×2					✓	✓	✓	✓	✓	✓	✓	✓
Microperimetry	✓	×2					✓	✓	✓	✓	✓	✓	✓	✓
Reading speed	✓	×2							✓	✓	✓	✓	✓	✓
Contrast Sensitivity	✓	×2							✓	✓	✓	✓	✓	✓
Electroretinography[j]	✓	✓							✓	✓		✓	✓[j]	✓
Optical Coherence Tomography	✓	×2					✓	✓	✓	✓	✓	✓	✓	✓
Fundus Photography		✓										✓		✓
Quality of life questionnaire	✓	✓							✓	✓	✓	✓	✓	✓

[a] The screening visit should occur within 3 months before study agent administration.
[b] The baseline (BL) visit should occur within 7 days before study agent administration.
[c] Long-term follow-up (LTFU) evaluations once a year for years 2-5.
[d] An early termination (ET) visit will be sought for any subject who withdraws from the study before the Year 1 visit. Perform the evaluations indicated as ✓* if the ET visit occurs before the last visit at which these tests are required.
[e] DNA testing for participants who have not had a mutation in the *RS1* gene documented previously.
[f] Physical exam, safety labs and coagulation may be obtained at either the screening or baseline exam.
[g] Safety labs include hematology and clinical chemistry as specified in Section **Error! Reference source not found.**.
[h] Clinical evaluation consists of an interim medical history, including use of carbonic anhydrase inhibitors and other medications, review of AEs, and a symptom-directed physical examination.
[i] Ophthalmic examinations include slit lamp examination, tonometry, indirect ophthalmoscopy and retinal biomicroscopy in both eyes will be evaluated at each visit, except on Day 0 (Visit 3) when the only required exam is tonometry of the study eye about 30 minutes after study agent administration is completed.
[j] ERG testing at LTFU visit if a significant change seen in ERG at month 12 visit compared to screening and baseline visits.

5. Study Treatment

All subjects will receive rAAV2tYF-CB-hRS1, a replication-incompetent, recombinant adeno-associated virus (rAAV) vector that expresses the RS1 protein after the vector enters retinal cells. The dose level of each group is described in the schematic of study design shown in section 4.1.

5.1 Method of Assigning Subjects to Treatment Groups

Male individuals with a diagnosis of XLRS, and a parent or guardian of children <18 years of age, are invited to give informed consent prior to screening procedures. After appropriate written informed consent/assent has been obtained, potential participants will then undergo an assessment of their medical history, physical examination, and selected clinical laboratory tests to ensure eligibility according to the protocol. Individuals who meet all inclusion and exclusion criteria are asked to join the study.

Refer to Section 4.1 for the method of assignment of subjects to treatment groups.

6. Sample Size and Power Considerations

No formal sample size calculations were performed. A sample size of 3 participants per group is typical of the dose escalation component in Phase 1/2 clinical trials of gene therapy products, especially for diseases with low prevalence. Up to 27 male individuals with XLRS will be enrolled in this study. This small sample size will obviously limit the power of the study, so that only very large treatment effects can be detected. For example, if no dose-limiting toxicity is detected among the first 9 participants, the 95% confidence interval for the rate of dose-limiting toxicity would be from 0 to 33.63%, and if no dose-limiting toxicity is detected among the maximum of 27 participants in the study, the 95% confidence interval for the rate of dose-limiting toxicity would be from 0 to 12.77%.

7. Data Preparation

Clinical data will be captured using an electronic case report form (eCRF) that will be completed for each subject by the investigator or designee.

Data from the eCRF and data from central laboratories will be entered into a computer database and further quality assurance checks will be made to produce a final database for analysis.

At the end of the study the investigator must sign and date a declaration attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject's participation in the study.

8. Analysis Population

The safety population will consist of all subjects who receive an intravitreal injection of the study agent. The safety population will be used for the data analyses with subjects grouped as treated.

The per protocol (PP) population is a subset of the safety population and includes the subjects who complete the study with no major protocol deviations. Major protocol deviations include inclusion/exclusion criteria deviations and use of prohibited medications. Additional analysis may be conducted on the PP population.

9. General Statistical Considerations

9.1 Unit of Analysis

The unit of analysis in this study will be the study eye for all applicable efficacy and safety summaries. In this study, only the study eye will receive treatment with the study drug. The study eye is defined as the eye with the worse visual acuity at the baseline visit. If both eyes have the same visual acuity, the choice of study eye will be determined at the discretion of the investigator in consultation with the participant. Additionally, non-ocular AEs and medical history will be presented at the subject level.

9.2 Missing or Inconclusive Data Handling

Missing data will be treated as missing and no imputation will be performed unless otherwise specified.

9.3 Definition of Baseline and Pretreatment

Values from the baseline visit (or an average for multiple baseline values) will be considered baseline values for any variables that are analyzed over time. If baseline visit data were not collected, then screening values will be used as baseline values. Pretreatment values will be all values collected at screening or baseline visits.

9.4 Data Analysis Conventions

All data analysis outlined in this SAP will be performed by Statistics & Data Corporation (SDC). 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 figures and Portable Document Format (PDF) for tables and listings using landscape orientation. All study data for treated subjects will be listed by group, subject, and visit (as applicable) unless otherwise specified. Only a disposition listing will be created for screen failed subjects.

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. 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 visit values minus the baseline value.

All statistical tests will be two-sided with alpha level of 0.05. Unless otherwise specified, summaries will be presented by group (1A, 1B, 2, 2A, 2+2A, 3, 4, 3+4, and all subjects) and, where appropriate, visit.

Unscheduled visits will not be summarized. Study visits will be referred to in all tables and listings with the expected study day/month/year corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. The following table shows the scheduled study visits, their planned study day:

Scheduled Visit	Planned Study Day
Visit 1	Screening
Visit 2	Baseline
Visit 3	Day 0
Visit 4	Day 1
Visit 5	Day 7
Visit 6	Day 14
Visit 7 Visit 8	Month 1 Month 2
Visit 9	Month 3
Visit 10 Visit 11 Visit 12 Visit 13 Visit 14 Visit 15 Visit 16	Month 6 Month 9 Month 12 Year 2 Year 3 Year 4 Year 5

10. Disposition of Subjects

The following disposition items will be summarized:

- The number of subjects screened (who signed the informed consent/assent form)
- The number of screen failures
- The number of subjects enrolled (who met the enrollment criteria)
- The number of subjects treated (who received an intravitreal injection of study agent)
- The number and percentage of subjects who completed the study
- The number and percentage of subjects who withdrew from the study and the reasons for premature discontinuation
- The number and percentage of subjects with any major deviations

All percentages will use the number of subjects treated as the denominator, unless indicated otherwise.

In addition, disposition and protocol deviation listings will be provided.

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, race, ethnicity, and genetic testing results.

Age (years) will be summarized, overall and by group, using continuous descriptive statistics. Age will also be summarized for the following categories: <=12, 13-18, 19-40, and >=41 years. Age will be reported in years and calculated using the following formula:

Age = Integer value of (Date of informed consent minus date of birth)/365.25

The number and percentage of subjects will be presented, overall and by group, for race and ethnicity.

A subject listing that includes all demographic variables and genetic testing results will be provided.

11.2 Pretreatment Variables

Pretreatment variables include height and weight, clinical variables (temperature, blood pressure, pulse, and respiratory rate), and physical examination results.

11.2.1 Physical Examination

A complete physical examination will be performed at the screening or baseline visit, to include examination of major organ systems (head/eyes/ears/nose/throat, neck, cardiovascular, respiratory, abdomen, musculoskeletal/extremities, skin, lymph nodes, and neurological).

A clinical evaluation, including a symptom-directed physical examination, will be obtained at all other visits.

A subject listing of physical examination abnormalities at baseline will be produced.

11.2.2 Vital Signs

Vital signs, including height, weight and BMI, will be summarized with continuous descriptive statistics at baseline. A subject listing of the vital signs results will also be produced.

12. Medical History and Concomitant Medications

12.1 Medical History

A medical history will be obtained at the screening visit.

A clinical evaluation, including an interim medical history, will be obtained at all other visits.

Medical history will be summarized using discrete summary statistics.

A listing of medical history will be generated.

12.2 Concomitant Medications

A clinical evaluation including use of carbonic anhydrase inhibitors (CAI) and other medications will be obtained at all post-screening. These medications will be considered concomitant as the data are collected during the course of the study.

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary, (Enhanced B2, March 2017) and summarized to the therapeutic drug class (anatomical therapeutic chemical [ATC] 4 classification) and preferred name (generally the brand/trade drug name).

Concomitant medications will be tabulated for each group using frequencies and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each group.

Concomitant medications and CAI use will be listed separately.

13. Treatment Exposure

13.1 Treatment Exposure

A subject listing of study agent administration will be produced.

14. Safety Analyses

14.1 Adverse Events

An 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 and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The occurrence of an AE may come to the attention of study personnel during study visits and interviews or by a study recipient presenting for medical care. All AEs must be graded for intensity and relationship to study product.

Every AE recorded in this study must be assessed by the investigator to determine whether or not it meets the definition of a dose-limiting toxicity (DLT). A DLT is defined as any toxicity determined by the investigator to be related to the study agent and deemed serious or sufficiently severe to preclude dose escalation. For the purpose of this study, any grade 4 or 5 event (per the Common Terminology Criteria for Adverse Events [CTCAE] v4.0 criteria) that is assessed as possibly, probably or definitely related to the study drug will be considered to be a DLT.

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

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 group. This summary will also include breakdowns of TEAEs further categorized as ocular (study eye, fellow eye, and both eyes separately) or non-ocular, Grade 3 or 4 local (ocular) or systemic AEs that occur during the 12 months after study agent administration, serious TEAEs (SAEs), TEAEs by maximum severity, TEAEs by maximum relationship to study agent, TEAEs by relationship to study agent injection procedure, 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 SOC and PT using MedDRA Version 20.0. Non-ocular TEAEs will be summarized by group at the subject level by SOC and PT. Ocular TEAEs will be similarly summarized at the subject level for study and fellow eyes separately. 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. In the summary, SOC will be listed in order of descending frequency for all subjects; PTs will be listed in order of descending frequency for all subjects within each SOC.

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

- Ocular TEAEs (study eye, fellow eyes, both eyes)
- Non-ocular TEAEs
- Grade 3 or 4 local (ocular) or systemic AEs that occur during the 12 months after study agent administration
- Ocular TEAEs related to study agent
- Non-ocular TEAEs related to study agent
- Ocular TEAEs related to intravitreal injection procedure
- Non-ocular TEAEs related to intravitreal injection procedure
- Serious TEAEs
- Serious TEAEs related to study agent
- Serious TEAEs related to intravitreal injection procedure

All AEs will be assessed by the investigator using the following guidelines to quantify intensity:

- Mild: Events that do not interfere with daily activities and require no medical intervention.
- Moderate: Events that cause some interference with daily activities and may require simple medical interventions.

- Severe: Events that prevent usual daily activities and require medical intervention.
- Life-threatening: Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.
- Fatal: Any AE that causes the death of the subject. Except for sudden and unexpected death, death is not an AE, but rather the event that caused the subject to die is the AE.

Summaries of TEAEs by maximum intensity 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 treatment 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 maximum severity.

The relationship of each AE to the study drug/intravitreal injection procedure should be determined by the Investigator using these explanations:

- Associated – The event is temporally related to the administration of the study agent/ intravitreal Injection procedure and no other etiology explains the event.
- Not Associated – The event is temporally independent of study agent intravitreal Injection procedure and/or the event appears to be explained by another etiology.

Events assessed as being associated with the study agent or associated with the intravitreal injection procedure will be further classified as possibly, probably or definitely related to study agent or injection procedure.

Events assessed as being not associated with study agent or injection procedure will be further classified as probably not or definitely not related to study agent or injection procedure.

All AEs will be presented in a by-subject listing. AEs leading to study treatment discontinuation, all serious AEs, and DLTs will also be presented in separate listings.

14.2 Clinical Laboratory Data

14.2.1 Hematology and Clinical Chemistries

Hematology and clinical chemistry will be obtained at the screening or baseline visit and at 7 and 14 days after study agent administration. Hematology will include hemoglobin, hematocrit, white blood cell count with differential and platelet count. Clinical chemistry will include sodium, potassium, chloride, total protein, albumin, calcium, phosphorous, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase.

The observed and change from baseline values of quantitative hematology and clinical chemistry parameters will be summarized by group at each visit with continuous descriptive statistics. Analyses will also include shifts from baseline to each post-baseline visit values using low, normal, and high classifications. Normal ranges will be used to determine the classifications. Values below the normal range will be classified as low, values above the normal range will be classified as high, and values within the normal range will be classified as normal.

Subject listings will be provided for hematology and clinical chemistries, separately, for each time point for all laboratory parameters and will include a column to distinguish abnormal values.

14.2.2 Coagulation

Coagulation tests (prothrombin time and partial thromboplastin time) will be obtained at the screening or baseline visit.

A subject listing will be provided for coagulation tests.

14.3 Immunology

Serum to measure antibodies to AAV will be obtained at the screening visit and at 1, 3, 6 and 12 months after study agent administration and at each long-term follow-up visit. Serum to measure antibodies to RS1 will be collected at the baseline visit and at 1, 3, and 12 months after study agent administration.

Peripheral blood mononuclear cells (PBMC) will be collected at the baseline visit and at 1, 2 and 3 months after study agent administration. Aliquots of these PBMC samples will be stored for possible future analyses including measurement of T cell responses to AAV or RS1.

Immune responses will be measured quantitatively (antibody titer, spot-forming cells per 10^6 PBMC) and also as binary indicators of whether there is a measurable response to the target protein.

The observed and change from baseline values of quantitative immunology parameters will be summarized by group at each visit and time point (where appropriate) with continuous descriptive statistics. The qualitative results will be summarized with categorical descriptive statistics.

A subject listing will be provided for immunology parameters.

14.4 Vector DNA Analysis

Whole blood for detection of vector DNA by PCR assay will be obtained at the baseline visit and at 1, 7 and 14 days after study agent administration.

A summary table and a subject listing will be provided for the vector analysis.

14.5 Slit-Lamp Biomicroscopy Examination

A dilated slit-lamp examination will be performed using the investigator's standard procedure. Documentation will include the presence or absence of central and peripheral schisis.

A slit-lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, and vitreous will be performed at each visit.

Shifts from baseline to worst value during follow-up will be tabulated. A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

14.6 Tonometry

Tonometry will be used to measure intraocular pressure (IOP). The observed and change from baseline values for IOP will be summarized for each eye using continuous descriptive statistics by visit for each group and for all subjects.

Subject listings of tonometry results will also be produced.

14.7 Indirect Ophthalmoscopy

An indirect ophthalmoscopy examination of the vitreous, disc, macula, vessels, lens, and periphery will be performed at each visit. Shifts from baseline to worst value during follow-up will be tabulated.

Subject listings of indirect ophthalmoscopy results will also be produced.

15. Efficacy Analyses

15.1 Visual Acuity

BCVA testing will be performed once at the screening visit, twice at the baseline visit, and once at each visit after study agent administration, including each long-term follow-up visit. BCVA will be determined using a standard ETDRS visual acuity testing protocol.

The observed and change and percent change from baseline (average of the two baseline results) visual acuity will be summarized for each eye using continuous descriptive statistics by visit for each group and for all subjects. P-values from paired t-tests comparing post-baseline visits with baseline visit and p-values from 2-sample t-tests comparing study eye with fellow eye will be presented for Treatment Groups 2A, 2+2A, 4, 3+4, and all subjects combined. All inferential statistics are

exploratory in nature. Visual acuity data will be presented as the letter score and the logMAR (calculated as (85-ETDRS)/50, where ETDRS is the ETDRS/EVA letter score) at each time point. Change from baseline in ETDRS letter score will be summarized for the following categories: <=-15, -15 to <-8, -8 to <0, no change, >0 to 8, >=8 to 15, >=15. A subject listing of visual acuity will also be produced.

Box plots of change from baseline in ETDRS BCVA by visit will be presented by group and overall (one box for each group side-by-side at each visit) and repeated by eye (study eye and fellow eye).

Line plots of ETDRS BCVA letter score by visit with 95% confidence intervals (CIs) will be plotted by group and overall. Right and left eyes will be displayed side-by-side on the same page.

Histograms of ETDRS BCVA score at each visit by group and overall will be presented in panel graphs (one panel for each group by visit) and repeated by eye (study eye and fellow eye).

Scatter plots of ETDRS BCVA score at follow-up visits versus baseline (also known as shift plots) by group and overall will be presented in panel graphs (one panel for each group by visit) and repeated by eye (study eye and fellow eye). A regression line and a line going through the origin will be overlaid in the scatter plots.

15.2 Spectral Domain Optical Coherence Tomography (SD-OCT)

Retinal anatomy will be evaluated by SD-OCT scans of both eyes once at the screening visit, twice at the baseline visit, and once at 1, 2, 3, 6, 9 and 12 months after study agent administration and at each long-term follow-up visit. Additional SD-OCT scans may be obtained at the discretion of the investigator. Each SD-OCT will generate macular volume scans and high resolution horizontal and vertical scans centered on the fovea.

The observed and change from baseline (average of the two baseline results) values for continuous SD-OCT parameters will be summarized for each eye using continuous descriptive statistics by visit for each group and for all subjects. In addition, percent change from baseline will be summarized for Cystic Cavity Volume (mm^3). The paired t-tests and graphs as specified in Section 15.1 will be created for all OCT parameters and two-sample t-tests comparing study eye with fellow eye will be performed only for Cystic Cavity Volume (mm^3). SD-OCT parameters include: Cystic Cavity Volume (mm^3), Macular Volume (mm^3), Central Segment (µm), Inner Circle Superior (µm), Inner Circle Nasal (µm), Inner Circle Inferior (µm), Inner Circle Temporal (µm), Outer Circle Superior (µm), Outer Circle Nasal (µm), Outer Circle Inferior (µm), and Outer Circle Temporal (µm). Categorical parameters will be summarized using counts and percentages for each group and for all subjects at each visit for each eye. Categorical parameters include: Ellipsoid zone evaluation over fovea, RPE disruption, is the EZ band present within the scans, were the scans obtained in follow up mode, was manual segmentation performed. A subject listing of SD-OCT results will also be produced.

15.3 Visual Field

Visual field testing will be performed once at the screening visit, twice at the baseline visit, once at 1, 2, 3, 6, 9, and 12 months after study agent administration, and once at each long-term follow-up visit. Visual field testing will be performed using the Haag Streit Octopus 900 perimeter. Static perimetry will use the German Adaptive Thresholding Estimation (GATE) method and kinetic perimetry will use the Semi-Automated Kinetic Perimetry (SKP) method.

The observed and change from baseline (average of the two baseline results) static and kinetic perimetry parameters will be summarized for each eye using continuous descriptive statistics by visit for each group and for all subjects. In addition, percent change from baseline will be summarized for 30-degree Hill of Vision (decibel steradians), Volume of Full Field Hill of Vision (decibel steradians), and Total Volume Loss (decibel steradians). The paired t-tests as specified in Section 15.1 will be created for all static and kinetic perimetry parameters and two-sample t-tests comparing study eye with fellow

eye will be performed only for 30-degree Hill of Vision (decibel steradians), Volume of Full Field Hill of Vision (decibel steradians), Total Volume Loss (decibel steradians), Mean Sensitivity, and Mean Defect. The same graphs as specified in Section 15.1 will be created for static perimetry. Static perimetry parameters include: 30-degree Hill of Vision (decibel steradians), Volume of Full Field Hill of Vision (decibel steradians), Total Volume Loss (decibel steradians), Reliability Factor, False Positive Ratio (%), and False Negative Ratio (%). Kinetic perimetry parameters include: I4e Isopter, I4e Scotoma, III4e Isopter, III4e Scotoma, V4e Isopter, and V4e Scotoma. Separate subject listings for static and kinetic perimetry will also be produced.

15.4 Microperimetry

Microperimetry testing will be performed using the MP1 microperimeter once at the screening visit, twice at the baseline visit, once at 1, 2, 3, 6, 9, and 12 months after study agent administration, and once at each long-term follow-up visit.

The observed and change from baseline (average of the two baseline results) values for continuous microperimetry parameters will be summarized for each eye using continuous descriptive statistics by visit for each group and for all subjects. The paired t-tests and figures as specified in Section 15.1 will be created. Continuous microperimetry parameters for include: Bivariate Contour Ellipse Area (BCEA) 95% Fixation Points (square degrees), Mean Sensitivity, Mean Defect, Percentage of Fixation Points within 2 Degrees, Percentage of Fixation Points within 4 Degrees, Percentage of Fixation Points Located Centrally, and Duration Time for Grid Testing; and Duration Time and BCEA 95% Fixation Points (Square Degrees) for 30 Second Fixation Test. Categorical parameters will be summarized using counts and percentages for each group and for all subjects at each visit for each eye. Categorical parameters include: fixation stability (Stable, relatively unstable, and unstable) and fixation location (predominantly central or predominantly eccentric). Percentages will be based on the number of subjects with responses. A subject listing of microperimetry results will also be produced.

15.5 Reading Speed

Reading speed will be performed once at the screening visit, twice at the baseline visit, and once at 3, 6, 9, and 12 months after study agent administration, and at each long-term follow-up visit. Reading speed will be measured using University of Minnesota trademark for low vision visual acuity (MNREAD) charts.

Reading Acuity (RA) is the smallest print size that the patient can read without making significant errors. RA is calculated as 1.4 - (sentences read x 0.1) - (number of words read incorrectly x 0.01), a method proposed by Patel et al[2].

Critical Print Size (CPS) is the smallest print size that supports reading speed at ≥ 80% of the mean reading speed at the preceding print sizes. Maximum Reading Speed (MRS) is the mean reading speed for all print sizes larger than the CPS.

The observed and change from baseline (average of the two baseline results) reading speed results (Maximum Reading Speed [WPM], Reading Acuity, Critical Print Size) will be summarized using continuous descriptive statistics by visit for each group and for all subjects. The paired t-tests and figures as specified in Section 15.1 will be created. A subject listing of reading speed results will also be produced.

15.6 Contrast Sensitivity

Contrast sensitivity testing will be performed once at the screening visit, twice at the baseline visit, and once at 3, 6, 9, and 12 months after study agent administration, and at each long-term follow-up visit. Contrast sensitivity will be measured using Pelli-Robson charts.

The observed and change from baseline (average of the two baseline results) log contrast sensitivity for each eye and both eyes will be summarized using continuous descriptive statistics by visit for each group and for all subjects. The paired t-tests and figures as specified in Section 15.1 will be created. A subject listing of contrast sensitivity testing results will also be produced.

15.7 Full-field and Multi-Focal Electroretinography

Electroretinography testing of both eyes will be performed at the screening and baseline visits and at 3, 6 and 12 months after study agent administration, using both ffERG and mfERG procedures.

If there is a significant change in the ERG at the 12-month visit compared to the ERG at the screening and baseline visits, the ERG will be repeated at the long-term follow-up visits.

The observed and change from baseline full-field and multi-focal ERG results will be summarized separately for each eye using continuous descriptive statistics by visit for each group and for all subjects. The paired t-tests and figures as specified in Section 15.1 will be created. Continuous parameters for full-field ERG include: Max B-wave (amplitude), Max A-wave (amplitude), Ratio of A-wave to B-wave (amplitudes), Dark-adapted response for B-wave alone at 0.01 flash (represents a pure B wave), Dark-adapted response for A-wave alone at 10 flash, Light-adapted 30 hz peak-to-peak amplitude. An additional assessment of ffERG responses will be performed using the method of Hood and Birch[1]. The amplitude of the leading edge of the a-wave will be determined from a set of three additional white flashes of 25, 50 and 100 cd/m2 presented under dark adapted and then light adapted conditions, by subtracting the light-adapted responses from the dark-adapted responses. The rod b-wave component will then be isolated by subtracting the rod a-wave from the ERGs to each of the three flash intensities. Continuous parameters for mullti-focal parameters include: Latency Ring 1 (ms), Latency Ring 2 (ms), Latency Ring 3 (ms), Latency Ring 4 (ms), Latency Ring 5 (ms), Latency Ring 6 (ms), Amplitude Ring 1

(nV/deg2), Amplitude Ring 2 (nV/deg2), Amplitude Ring 3 (nV/deg2), Amplitude Ring 4 (nV/deg2), Amplitude Ring 5 (nV/deg2), Amplitude Ring 6 (nV/deg2) and sum of amplitude of all rings. Subject listings of full-field and mfERG results will also be produced.

15.8 Quality of Life Analyses

15.8.1 25-Question Visual Function Questionnaire (VFQ-25)

For participants ≥ 16 years of age, the 25-question visual function questionnaire (VFQ-25) overall composite score and the following sub-scale scores will be calculated based on the VFQ-25 Manual.

The VFQ-25 is scored according to the following table:

Item Numbers	Original Response Category	Score for Analysis
1,3,4,15c [(a)]	1 2 3 4 5	100 75 50 25 0
2	1 2 3 4 5 6	100 80 60 40 20 0
5,6,7,8,9,10,11,12,13,14,16,16a	1 2 3 4 5 6	100 75 50 25 0 *
17,18,19,20,21,22,23,24,25	1 2 3 4 5	0 25 50 75 100

(a) 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.

* 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."

Next create the VFQ-25 Sub-scales by averaging non-missing assigned scores as indicated in the following table:

Sub-scale	Number of Items	Items to be averaged (after recoding)
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

The mean of the sub-scale items is the sub-scale score. The VFQ-25 composite score is the mean of the sub-scale scores.

Descriptive statistics for the scores will be used to summarize the overall composite score and sub-scale scores at each study visit. The change in the overall composite score and sub-scale scores from the baseline visit to each follow-up visit will also be summarized. The paired t-tests as specified in Section 15.1 will be created.

Two listings will be prepared. One listing displaying the sub-scales and composite score at each visit will be produced. The second listing will display the original response categories for each item at each visit for each patient.

15.8.2 Functional Vision Questionnaire for Children and Young People (FVQ_CYP)

For participants < 16 years of age, the Functional Vision Questionnaire for Children and Young People (FVQ_CYP) summary score and the sub-scale scores will be calculated based on the FVQ_CYP manual.

The FVQ_CYP (36) summary score will be calculated by converting the response categories 1-4 to 0-3 scores and adding the scores on the 36 items. A higher summary score denotes a higher level of functional difficulty. A pro-rated summary score will not be calculated for a respondent who omitted answers to more than 20% of the questionnaire items (8 out of 36 items).

Descriptive statistics for the score will be used to summarize the summary score at each study visit. The change in the summary score and sub-scale scores from the baseline visit to each follow-up visit will also be summarized. The same inferential statistics as specified in Section 15.1 will be created.

A listing displaying the summary score and original response categories at each visit will be produced.

15.9 Fundus Photography

Fundus photography will be performed at the baseline visit and at the visit 12 months after study agent administration.

The results will be summarized using counts and percentages for each group and for all subjects at each visit for each eye. Percentages will be based on the number of subjects with responses. Fundus

photography parameters include Any evidence of increased inflammation, Hemorrhage, Retinal detachment, Is there RPE disturbance or atrophy in the fovea, Any changes from baseline visit. A subject listing of the fundus photograph parameters will also be produced.

16. Long-term Follow-Up (LTFU)

After the completion of 9 study visits over the course of one year after study agent administration, long-term follow-up (LTFU) will be conducted annually for an additional 4 years after the Month 12 visit. In accordance with regulatory guidance for gene therapy clinical trials, information will be obtained about any cancer, neurological, autoimmune or hematological disorder that developed or worsened since the last visit. A subject listing containing this information will be provided.

17. Interim Analysis

No interim analysis will be conducted for this study. Preliminary analyses of available data may be conducted during the study.

18. Data and Safety Monitoring Committee

Refer to section 4.1.

19. Changes from Protocol-Stated Analyses

- Change over time in titers of serum antibodies and IFN-γ ELISPOT responses to retinoschisin (RS1) is moved from secondary safety outcomes to other outcomes.
- Inferential statistics for all efficacy endpoints will be calculated.
- Visual field parameter (square root of the loss variance) will not be read by the Reading Center.

20. References

[1] Hood DC and Birch DB. *A computational model of the amplitude and implicit time of the b-wave of the human ERG*. Vis Neurosci 1992;8:107-26

[2] Patel PJ, Chen FK, Da Cruz L, Rubin GS, and Tufail A. *Test-retest variability of reading performance metrics using MNREAD in patients with age-related macular degeneration*. Invest Ophthalmol Vis Sci 2011;52:3854-9

21. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

22. Tables

Table Number	Title
Table 14.1.1	Subject Disposition
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23. Listings

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Listing 16.2.6.10.1	25-Question Visual Function Questionnaire (VFQ-25) – Overall and SuB-Scale Scores

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