A Phase 1/2 Safety Study in Subjects with CHM (Choroideremia) Gene Mutations Using an Adeno-Associated Virus Serotype 2 Vector to Deliver the Normal Human CHM Gene [AAV2-hCHM] to the Retina

Protocol Number: AAV2-hCHM-101

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STATISTICAL ANALYSIS PLAN

Version 3.0

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STATISTICAL ANALYSIS PLAN
Version 3.0

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SAP Revisions

Version 1.0 of the SAP was finalized at the time of Protocol version 4.0 (13NOV2014). The following table details the changes made to the SAP due to subsequent protocol amendments.

Protocol Version #	SAP Section	Modification	Description and Rationale
5.0	2.2.2	Modified the research laboratory results for Safety Evaluation by removing REP-1 antibody, and changing PBMC to Whole blood	REP-1 antibody assay was removed from protocol v5. PBMC was changed to Whole blood for PCR analysis (vector shedding) in protocol v5.
5.0	3.1	Modified the dosing schedules: with at least 2 weeks between vector administrations to successive subjects for the first two subjects of a given dose group (study-wide) and at least 2 weeks between vector administrations per clinical site for the rest of the subjects in the given dose group	A new clinical site was added for Dose Group 2 and the dosing schedules were modified in the protocol v5.
5.0	6.1.3	Added the reading speed (wpm), maximum reading speed (wpm), and critical print size to the data listing.	MNREAD test for reading speed test was added to CRF. Modified the SAP to reflect this change.
5.0	7	Removed REP-1 antibody from safety analysis	REP-1 antibody assay was removed from protocol v5.
6.0	3.1	Changed the number of subjects from 5 to 10 for Dose Group 2.	Additional 5 subjects were added for cohort 2 in protocol v6.
6.0	2.2.1 & 6.1.8	Removed the Pupillometry	Pupillometry was removed from protocol v6.
6.0	4.3	Changed study day for Year 2 from 731 to 730 Added a paragraph for long-term follow-up visit windows	Updated to match protocol.
7.0, 8.0	2.2.1	Added Goldmann Visual Field Test Added Octopus perimetry	Post-baseline visits at Year 2 and long term follow up were added for Goldmann visual field test. Octopus perimetry was added to the protocol v7.
7.0, 8.0	6.1.2	Added Goldmann Visual Field Test Added Octopus perimetry	Updated to match the protocol.
8.0	5.3	Removed Goldmann visual field test	Post-baseline visits at Year 2 and long term follow up were added for Goldmann visual field test. So moved this test to

Protocol Version #	SAP Section	Modification	Description and Rationale
			Section 6.1.2.
8.0	7.3	Modified the sentence to "Laboratory values will be presented in the data listings."	Modified to be consistent with Section 4.3.
8.0	All	Changed "study drug" to "investigational product"	Updated to match the protocol.
8.0	Appendix A	Updated Schedule of Assessments	Used the new Schedule of Assessment in protocol v8.

Version 2.0 of the SAP was finalized at the time of Protocol version 8.0 (27APR2017). The following table details the changes made to the SAP version 2.0 to match protocol amendment v10.0.

Protocol Version #	SAP Section	Modification	Description and Rationale
10.0	Appendix A	Removed Years 6-15 of long-term follow up from the schedule of assessments.	Updated to match protocol.
10.0	3.1	Changed 13 years of additional long-term follow up to 3 years.	Updated to match protocol.
10.0	4.3	Changed annual follow-up for Years 4-15 to Years 3-5	Updated to match protocol.

1. INTRODUCTION

Choroideremia is a degenerative retinal disease for which gene transfer research is in progress, including a clinical trial in the United Kingdom (MacLaren *et al.,* 2014). This X-linked disease of males is characterized by deletions or mutations in the choroideremia gene (*CHM*) at Xq21.2, resulting in defective or absent Rab escort protein-1 (REP-1), the encoded protein of the *CHM* gene (Nussbaum *et al.,* 1985; Seabra *et al.,* 1993; Seabra *et al.,* 1995; Cremers *et al.,* 1994; Alexandrov *et al.,* 1994). Absence or deficiency of REP-1 due to deletions or mutations in the *CHM* gene leads to cellular apoptosis and degeneration of the retinal pigment epithelium (RPE), choroid, and retinal photoreceptors. Although in normal retinas, the *CHM* gene is expressed in multiple cell types, including retinal pigment epithelium, photoreceptors and choroidal cells, there is evidence that the RPE cell is the primary disease causing cell type. The AAV serotype 2 vector, which targets RPE cells primarily (and other retinal cell types secondarily) is thus an ideal vector for choroideremia.

Clinically, choroideremia is diagnosed in affected males who manifest night blindness in childhood, followed by progressive constriction of visual fields, usually symptomatic in their teenage years, and eventual total blindness. The pathological hallmarks of the disease are degeneration of the choroicapillaris, as well as retinal pigment epithelium and photoreceptors (MacDonald *et al.,* 2009). The disease course is variable, with early manifestations of decreased dark adaptation, progressing to decreased peripheral vision, followed eventually by loss of central vision, generally occurring later in life. In some patients, blindness occurs after a prolonged course. The rationale for a gene transfer approach for choroideremia is that a corrective gene delivered to the RPE early enough in the clinical course may halt degeneration and restore the RPE, retinal vasculature, and photoreceptors.

This clinical study proposes to deliver the normal human *CHM* gene (hCHM) to the subretinal space using AAV2-hCHM, a single stranded AAV vector, based on several considerations.

This document details the statistical methods planned to perform the final analysis, as well as the interim Data Safety Monitoring Board (DSMB) analyses, of the Protocol AAV2-hCHM-101 study. The study is designed primarily to evaluate the safety and tolerability of subretinal administration of AAV2-hCHM, in an inter-subject group dose escalation in individuals with choroideremia.

2. OBJECTIVES AND EVALUATIONS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the safety and tolerability of subretinal administration, in an inter-subject group dose escalation, of AAV2-hCHM in adults with choroideremia.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To define the dose of AAV2-hCHM required to achieve stable, or improved visual function and functional vision in subjects with choroideremia.
- To characterize the immune responses to the *CHM* transgene protein product (REP-1) and AAV2 capsid proteins following subretinal administration of AAV2-hCHM.

2.2 Evaluations

2.2.1 Efficacy Evaluations

- Visual/retinal function evaluation:
    - Visual acuity
    - Goldmann Visual Field Test (III4e isopter)
    - Humphrey visual field tests
    - Octopus kinetic visual field test (for subjects whose central visual field is >20° in at least 1 of the 24 meridians at the Screening/Baseline visit using Goldmann perimetry III4e isopter)
    - Reading speed
    - Contrast sensitivity
    - Color vision test
    - Microperimetry
    - Full-field light sensitivity threshold testing
- Imaging:
    - Fundus photography
    - Optical Coherence Tomography (OCT)
- Evaluation of activities of daily life:
    - Quality of Life (QOL) questionnaire

2.2.2 Safety Evaluations

- Safety and tolerability assessments including but not limited to:

  a) Adverse events (AEs)

  b) Clinical laboratory results
    - Hematology
    - Chemistry panel
    - Urinalysis

  c) Research laboratory results:

- AAV Viral Capsid antibody
- Peripheral blood mononuclear cells (PBMC) for ELISpot assay
- Whole blood, serum and tears for vector sequences

d) Physical exams and vital signs

e) Ophthalmic examinations using standard instruments and methods

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is an open label, non-randomized, inter-subject dose escalation safety study (Phase 1/2) of two vector doses (up to $5x10^{10}$ vg per eye (Dose Group 1) and up to $1x10^{11}$ vg per eye (Dose Group 2)) administered unilaterally, with at least 2 weeks between vector administrations to successive subjects for the first two subjects of a given dose group (study-wide) and at least 2 weeks between vector administrations per clinical site for the rest of the subjects in the given dose group. The eye with worse visual acuity will be injected, unless the subject prefers that eye, in which case the contralateral (non-preferred) eye will be injected.

Five subjects will be entered to Dose Group 1 and ten to Dose Group 2. All subjects must meet entry criteria detailed in the Protocol Section 3.4. Dose escalation will be contingent upon DSMB review of the safety data through at least 30 days for all subjects in the prior cohort. Subjects will be followed up for safety and efficacy evaluations for approximately 2 years post vector administration, then additional 3 years of long-term follow-up. See Appendix A for the Schedule of Assessments.

3.2 Investigational Product Administration

3.2.1 Randomization Scheme and Study Arm Assignment

There is no randomization. All subjects will receive investigational product.

3.2.2 Blinding

Not applicable. This is an open-label study.

3.2.3 Dosing Schedule

Subjects in the first cohort will be dosed with AAV2-hCHM unilaterally by single subretinal vector delivery at up to $5x10^{10}$ vg per eye. There will be a minimum two-week interval between subject injections. In the absence of vector-related safety concerns following DSMB review of cohort 1 data through at least a minimum of 30 days post administration, cohort 2 subjects will be dosed at up to $1x10^{11}$ vg per eye.

3.2.4 Subject Compliance

Subjects may withdraw from the study at any time without prejudice to their care. As much as is feasible, the study team will follow subjects after investigational product administration since this gene transfer study offers the potential of single-use, long-term treatment that cannot be practically withdrawn.

It will be documented whether or not each subject completes the clinical study, and the reason for study discontinuation including: adverse event; consent withdrawn; death; lost to follow-up; physician decision; technical problem; request for termination by Sponsor or Regulatory Authorities; and administrative or other reason. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, the SAE will be recorded in the source documents and entered in the study CRF. If the subject withdraws, the study procedures to be done are identical to those of the Year 2 visit evaluations.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Due to the small sample size there are no statistical hypotheses regarding treatment effects. Rather, displays and comparisons of study results – regarding dose-related safety and efficacy among the dose cohorts – will primarily utilize descriptive statistics, as noted below.

Unless otherwise specified, continuous variables will be summarized by presenting the number of non-missing observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by presenting the number and percentage of subjects for each category.

Summary results will be provided for each dose cohort. All tabulations will be based on pooled data across study sites.

Analyses will be performed using SAS for Windows statistical software, version 9.2 or higher (SAS, Cary, NC), except where other software may be deemed more appropriate.

CTI will perform all efficacy and safety statistical analyses.

Subject data will be listed, sorted by dose cohort and subject number.

4.1 Data Quality Assurance

Spark, or its designated representative, will conduct a pre-study visit for each study site to verify the qualifications of the investigator, inspect study site facilities, become familiarized with site staff assigned to the study, and inform the investigator of responsibilities and procedures for ensuring correct study documentation.

A study coordinator at the study site will enter subject data into a remote data capture database (RDC) by completing electronic case report forms (eCRFs). All information recorded in the eCRFs for this study must be consistent with the investigator's source documentation for the study subjects. The study site will make available source documents to CTI personnel monitoring the study. The study monitor will verify consent of all subjects to participate in the study and will perform 100% source document verification of the eCRF data.

A CTI Clinical Data Associate (CDA) will review the data for discrepancies via programmed electronic consistency checks, data listings, or manually. Any discrepancies discovered via the data review process will be issued as queries in the RDC system to the study site for resolution. Once all the source verification is complete, all queries are resolved, and the database has been updated appropriately, the database will be locked and made available to CTI Biostatistics for final analysis. Data may be pulled by CTI Biostatistics for DSMB analysis at a time when source verification and query resolution is ongoing.

All SAS programs used to create analysis datasets and output will be validated by ensuring that the ".log" files are void of all errors, warnings and notes indicative of problems. Additionally, each program will be checked to ensure that it performs according to the program specification. All programs are developed and validated by separate members of the CTI Biostatistics Department.

When performing a quality control (QC) review of listings and tables output from SAS, it is not always possible to perform a 100% QC review of all fields. If a 100% QC review is not to be performed, the sample size of fields to undergo QC review may be determined by utilizing American National Standards Institute (ANSI) sampling procedures. Sampling procedures are conducted using "normal" inspection criteria (Inspection Level II, Single, and Normal) and an Acceptable Quality Level (AQL) of 0.010%. The following shows the sampling criteria:

Single Normal sampling procedure for Acceptable Quality Level (AQL) 0.010%

Number of Fields	Sample Size	Accept/Reject Criteria
2-8	2	0/1
9-15	3	0/1
16-25	5	0/1
26-50	8	0/1
51-90	13	0/1
91-150	20	0/1
151-280	32	0/1
281-500	50	0/1
501-1,200	80	0/1
1,201-3,200	125	0/1
3,201-10,000	200	0/1
10,001-35,000	315	0/1
35,001-150,000	500	0/1
150,001-500,000	800	0/1
500,001-up	1,250	0/1

4.2 Analysis Sets

The full analysis set (FAS) is defined as all subjects who have received the investigational product. All efficacy and safety analyses will be performed on the FAS.

4.3 Assessment Windows

For the purpose of listing and summarizing data, the time-in-study for each subject observation will be defined using study days. Such days will be measured relative to Day 0, the day in which the investigational product is received. Because protocol-specified visits (e.g., Day 30) will not necessarily occur on the same study day for all subjects, study visits will be defined through the use of windows. Study visits will have windows as per the following schema:

Study Visit	Visit and Laboratory Testing Window
Study Day 0	Day of investigational product administration
Study Day 1	No window
Study Day 14	14 ± 2 days
Study Day 30	30 ± 5 days
Study Day 90	90 ± 30 days
Study Day 180	180 ± 30 days
Study Day 365	365 ± 30 days
Year 1.5	547 ± 30 days
Year 2	730± 60 days

For evaluations after Year 2, the subject will go into the long-term follow-up phase. The subject returns to the clinic for follow-up at Years 2.5 and then annual follow-up, done in the clinic, for Years 3-5 for safety evaluations, standard ophthalmologic examinations, and retinal/visual function tests. The windows for the long-term follow-up visits are ± 60 days.

All data will be summarized by visit based on the visit in which the data was recorded in the database.

Baseline will be defined as the last pretreatment value during the screening period. If a repeat laboratory sample was drawn for a visit, only the repeat sample values will be listed or summarized. If there are repeated visual tests within the same visit, the average of all test results will be used for summary analysis. If there are more than one screening/baseline visit, the result from the later visit will be used for the analysis. Visual test results from all visits will be listed.

4.4 Handling of Dropouts or Missing Data

Missing data will remain missing. No imputation of missing data will be performed.

4.5 Multiple Comparisons

No multiple comparisons are planned for this study.

4.6 Data Derivations and Transformations

Not applicable.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

A table of counts of all enrolled subjects will be provided. Reasons for not completing study medication as planned and reasons for premature withdrawal will be tabulated for each dose cohort.

5.2 Protocol Deviations

A listing of all protocol deviations will be provided.

5.3 Demographic and Baseline Characteristics

All demographic characteristics including age, gender, race, ethnicity, height, and weight will be summarized using the FAS for the cohorts. Baseline characteristics including abnormalities of past ocular history for both injected and control eyes, and genetic analysis of *CHM* gene will be summarized and listed using the FAS. HIV test will be provided in a data listing.

5.4 Medical History

All medical conditions and surgical procedures will be classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percent of subjects with each medical condition and surgical procedure will be presented for each SOC and PT for the FAS subjects.

5.5 Prior and Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) drug classifications. The number and percent of FAS subjects using concomitant medications will be tabulated by default Anatomical, Therapeutic, and Chemical (ATC) class and by preferred name.

6. EFFICACY ANALYSIS

Safety is the primary objective of this study. All efficacy analyses are strictly exploratory.

6.1 Exploratory Efficacy Analyses

Each of the exploratory efficacy evaluations, which are described below, will be listed by injected and control eyes for each subject at each visit, grouped by cohort. The time points of each parameter assessments are presented in the Appendix A.

6.1.1 Visual Acuity

Visual acuity measures will document any change in central vision, the ability to resolve standard optotype images presented as optotypes/letters corresponding to different visual angles, *i.e.,* image size. This testing will use ETDRS charts. The level of central visual resolution is converted to a visual angle score (LogMAR) for comparison purposes. The reliability of the results, calculated visual acuity, LogMAR acuity score, and the method used for no optotype recognition will be listed for each tested distance.

6.1.2 Visual Field Tests

Visual field parameters will evaluate alterations in function of different regions of the retina; kinetic fields will be measured with Goldmann (III4e isopter), and Humphrey static fields with computerized testing, including foveal and macular thresholds, and a central field. In addition, Octopus kinetic perimetry will be done to subjects whose central visual field is >20° in at least 1 of the 24 meridians at Screening/Baseline visit using Goldmann perimetry III4e isopter.

Results from Goldmann visual field test: the reliability of the results, the total number of degrees

for all 24 meridians using the III4e test stimulus, and the number of the 24 meridians < 30° will be listed.

A list of Humphrey visual field test results will be presented for the variables including the reliability of the results, mean deviation, mean threshold, and foveal sensitivity from Humphrey 30-2 test and10-2 test.

A list of Octopus kinetic visual field test results will be presented for the variables including III4e visual field, III4e scotomas, V4e visual field, V4e scotomas, reaction time, duration, and reliability.

6.1.3 Reading Speed

The reading speed test will require subjects to read designated word slides with different levels of contrast between letters and background aloud and subsequently, the reading accuracy and speed will be reported. The time (seconds), number of words missed, number of extra words read, number of times re-read words, and the reason for not passing the test, if applicable, will be listed for each slide. Additionally, the reading speed (wpm), maximum reading speed (wpm), and critical print size will also be listed if the Minnesota Low-Vision Reading (MNREAD) test was performed.

6.1.4 Contrast Sensitivity

Contrast sensitivity will measure the subject's ability to discern targets presented at varying levels of contrast. The variables of measurements include the log contrast sensitivity and the pupil diameter.

6.1.5 Color Vision Test

Color vision testing will be conducted and the results will be listed at each visit.

6.1.6 Microperimetry

Microperimetry will be conducted in the dark-adapted state to evaluate maximal retinal sensitivity. Microperimetry measurements of the injected eyes will also be compared to the control (uninjected) eyes. The mean macula threshold and foveal sensitivity will be presented in a data listing.

6.1.7 Full-field Light Sensitivity Threshold Testing

Full-field light sensitivity threshold (FST) testing measures the light sensitivity of the entire visual field by recording the luminance at which a subject reports seeing the dimmest flash. The light sensitivity of each eye is measured separately by removing patches from one eye (and then the other). A sound is generated at the time of the light flash and the subject presses one button when they see a flash or a second button if they do not see a flash. Flashes of varying luminance (in a range spanning ~100 dB) are presented in a randomized order, except that the series starts with dim flashes. From this data, an algorithm calculates the minimum luminance (for each eye) at which the subject perceives light.

The results of light sensitivity measurements from each test, and the average of all reliable tests results will be listed for each of the light sources (White, Red, and Blue lights).

6.1.8 Fundus Photography

Fundoscopy will be performed with indirect ophthalmoscopic exam and fundus biomicroscopy. Photographs will be taken with a fundus camera following standard clinical methods. The variables including the interpretability of the photograph, the reason not interpretable, the area of retina without confluent atrophy, and the estimated area of intact RPE in disc areas will be listed.

6.1.9 Optical Coherence Tomography (OCT)

OCT captures micrometer-resolution, three-dimensional images from within optical scattering media (*e.g.,* retinal tissue). The Heidelberg Spectralis OCT machine will be used. Optical coherence tomography is an interferometric technique, typically employing near-infrared light. The use of relatively long wavelength light allows it to penetrate into the scattering medium, providing important images, including the thickness of the retina. The listed variables will include the reliability of the fast macular thickness map scan, the reason for unreliable scan, foveal thickness, macular volume, and the presence of subretinal and intraretinal fluid.

6.1.10 Quality of Life (QOL) Questionnaire

The Investigators will use a QOL questionnaire relevant to the subject population and a final score will be calculated. The final score (average of all numeric responses) will be listed at each visit.

6.2 Pharmacokinetic Analysis

No pharmacokinetic analysis is planned for this study.

7. SAFETY ANALYSIS

Safety assessments will include adverse events, clinical chemistry, hematology (complete blood count and differential), urinalysis, AAV viral capsid antibody, PBMC for ELISpot, vector shedding assessment, ophthalmic examination, vital signs, and physical examination.

All safety summaries (or analyses if applicable) will be conducted using the FAS. No formal hypothesis testing will be performed to compare differences between the cohorts.

7.1 Extent of Exposure

The actual dose received, estimated sub-retinal volume injected, estimated air fluid exchange, total number of injection-retinotomy sites, and the total number of successful injection-retinotomy sites will be summarized for each dose cohort. A listing of the data will also be presented.

7.2 Adverse Events

All adverse events (AEs) including serious adverse events (SAEs) will be recorded through the Year 2 visit following investigational product administration. Following the scheduled Year 2 visit, adverse event recording will occur for any related serious adverse events, or for the development of any oncologic, hematologic, neurologic or autoimmune events.

An AE is any untoward, undesired, or unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a subject participating in a clinical study with the Sponsor's investigational product, regardless of causal relationship. AEs will

include any conditions that: 1) were not present prior to investigational product administration, but appeared following investigational product administration; or 2) were present prior to investigational product administration, but worsened in severity and/or frequency following investigational product administration.

7.2.1 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is an adverse event which occurs on or after the date of investigational product administration.

7.2.2 Adverse Event Severity

Please refer to Protocol Number AAV2-hCHM-101, Version 4.0, 13Nov2015, Section 8.5, page 36 for details.

7.2.3 Adverse Event Relationship to Study Medication

Please refer to Protocol Number AAV2-hCHM-101, Version 4.0, 13Nov2015, Section 8.6, page 36 for details.

7.2.4 Serious Adverse Events

Please refer to Protocol Number AAV2-hCHM-101, Version 4.0, 13Nov2015, Section 8.4, page 35 for details.

7.2.5 Adverse Event Summaries

All AEs (serious and non-serious) occurring after investigational product administration and before the end of study, regardless of relationship to investigational product, will be included and classified by SOC and PT using MedDRA.

For treatment-emergent AEs (TEAEs), the following will be summarized and presented for the FAS subjects:

i. the number and percentage of subjects experiencing a TEAE by SOC, PT and the greatest intensity

ii. the number and percentage of subjects experiencing a TESAE by SOC and PT

In the summary tables, the incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the total number of subjects in the FAS. Thus, the incidence of TEAEs is shown in terms of the total number of subjects and not in terms of the total number of episodes. If a subject has repeated episodes of a particular TEAE, only the most severe episode, or the episode with the strongest causal relationship to investigational product, will be counted in the summary tables.

A subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing TEAEs in that particular SOC. Since a subject could have more than one type of TEAE within a particular SOC, the sum of subjects experiencing different TEAEs within the SOC could appear larger than the total number of subjects experiencing TEAEs in that SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted

only once in the total number of subjects experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each subject, grouped by dose cohort. The listing will contain the following information: dose cohort, verbatim term, SOC, PT, severity, relationship to study medication/surgical procedure/study measure, date and day of onset, date and day of resolution, treatment given to treat the adverse event, the outcome, whether the event was an SAE, whether it led to withdrawal and whether it is a TEAE. Listings will be sorted by subject identification number, onset date, SOC, and PT. If the onset date is completely missing, then these events will be presented first. If the onset date is missing a month or a day, then these events will be presented before any complete dates.

7.3 Clinical Laboratory Assessments

Laboratory assessments for hematology with differential, serum chemistries, urinalysis, AAV viral capsid antibody, PBMC for ELISpot, and vector shedding will be performed in accordance to the Schedule of Assessments in Appendix A.

Laboratory values will be presented in the data listings.

7.4 Ophthalmic Examination

Ophthalmic examinations using standard instruments and methods will be performed at Screening/Baseline and post-vector administration on Days 1, 3, 7 (if needed), 14, 30, 90, 180, 365, and Years 1.5 and 2. A listing of the status of normality, the grade (1-4) of abnormality, and the relationship of abnormality to the procedure and AAV2-hCHM (post-vector administration visits only) will be presented for each ocular system.

7.5 Vital Signs

Vital sign data including blood pressure, heart rate, respiratory rate, and body temperature will be presented in a data listing.

7.6 Physical Examination

The number and percentage of subjects with normal and abnormal physical examination findings will be summarized for each body system at each visit by cohort. A listing of abnormalities will also be provided.

7.7 Injection Site

The information of injection site number, correspondence with viable RPE, percentage of viable RPE exposed to the reagent, distance from fovea, entry point in relation to fovea, area of subretinal bleb, the fraction of total bleb area for each location of bleb in relation to fovea, whether the bleb was within macular arcades and whether is subfoveal will be provided in a data listing for each dose cohort.

8. DSMB COHORT REVIEW

In this trial, dose escalation will be contingent upon DSMB approval following review of the safety and efficacy data through at least 30 days for all subjects in the prior cohort. The data for DSMB analysis will be presented as described above. Following each DSMB meeting, the DSMB will

provide the Sponsor with written recommendations related to continuing, changing, or terminating the trial.

9. SAMPLE SIZE AND POWER CALCULATIONS

Sample size is based on clinical experience and precedent established for studies of similar design. Power calculations were not used to derive the sample size necessary for statistical comparisons.

10. REFERENCES

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11. APPENDICES

11.1 Appendix A: Schedule of Assessments

Table of Clinical Assessments	**Day**										**Year**			
Evaluations Follow Signing of Informed Consent Form	**Screening/ Baseline** Within 90 days of Day 0	0	1	3[1]	7[1]	14	30	90	180	365	1.5	2	2.5	3-5
(Acceptable window for visit, ± Days)				+1		± 2	± 5	± 30	±30	±30	±30	±60	±60	±60
Sequence Analysis of *CHM* gene (if not previously available), may be more than 90 days prior to Day 0	X													
History and physical exam	X									X		X		X
Vital Signs	X	X	X	X	X[1]	X								
Hematology	X	X	X	X		X	X	X		X		X		X
Chemistry	X	X	X	X		X	X	X		X		X		X
Virology	X													
AAV antibodies	X						X	X		X		X		
PBMC Collection	X						X	X		X		X		
Peripheral blood and tear PCR[2]	X	X	X	X		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		
Urinalysis	X	X	X	X		X				X		X		X
Ophthalmic Examination[1]	X		X	X[1]	X[1]	X	X	X	X	X	X	X	X	X
Visual Acuity	X		X	X	X[1]	X	X	X	X	X	X	X	X	X
Visual Field Test, Humphrey	X						X	X	X	X	X	X	X	X
Visual Field Test, Goldmann	X											X		X
Visual Field Test, Octopus[4]	X[4]						X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]
Reading Speed	X						X	X	X	X	X	X	X	X
Contrast Sensitivity	X						X	X	X	X	X	X	X	X
Color Vision Test	X						X	X	X	X	X	X	X	X
Microperimetry	X						X	X	X	X	X	X	X	X
Full-Field Light Sensitivity Threshold Testing	X						X	X	X	X	X	X	X	X[4]
Fundus Photography (with low intensity autofluorescence)	X						X	X	X	X	X	X	X	X
OCT	X						X	X	X	X	X	X	X	X
Quality of Life Questionnaire	X						X	X	X	X	X	X	X	X
Administration of AAV2-hCHM[3]		X												
AE Recording	X	X	X	X[1]	X[1]	X	X	X	X	X	X	X	X	X
Partner Pregnancy Outcome Recording										X	X	X	X	X
Concomitant Medication Recording	X	X	X	X[1]	X[1]	X	X	X	X	X	X	X	X	X

Notes for Table of Clinical Assessments:

[1] Day 7 evaluations, including an additional ophthalmic exam, will only be conducted if ocular inflammation is present at the Day 3 visit

[2] Blood/tear polymerase chain reaction (PCR) will be continued until two consecutive specimens test negative: Tear and blood collection will occur at each study visit until this result is obtained

[3] Day 0 = Day of vector administration: Unilateral subretinal dosing of AAV2-hCHM is conducted in the subject's non-preferred eye (or the eye with worse visual acuity if the subject does not have a preference) starting sequentially first with the Dose Group 1 (subjects #1-5, up to $5x10^{10}$ vg/eye) followed by Dose Group 2 (subjects #6-15, up to $1x10^{11}$ vg/eye). It should be noted that the degenerative component of the disease may preclude delivery of the full dose, in which case the dose given will be based on vector concentration and total volume administered (up to 300 µL).

[4] Octopus kinetic visual field test will only be done to subjects whose central visual field is >20° in at least 1 of the 24 meridians at the Screening/Baseline visit using Goldmann perimetry III4e isopter.