COVER PAGE

Official Title:	A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)
NCT Number:	NCT03496012
Document Date:	Protocol Version 5.0: 15 March 2019

CLINICAL STUDY PROTOCOL
NSR-REP-01 (TIMREPIGENE EMPARVOVEC)

AAV2-REP1

A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)

STAR Study

INDICATION: Choroideremia

STUDY PHASE: 3

EUDRACT NUMBER: 2015-003958-41

Clintrials.gov NCT03496012

SPONSOR: NightstaRx Ltd
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London W1T 5BJ UK
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ORIGINAL PROTOCOL DATE: 17 September 2015
DATE OF AMENDMENT 1: 10 November 2015
DATE OF AMENDMENT 2: 26 February 2016
DATE OF AMENDMENT 3: 01 August 2017
DATE OF AMENDMENT 4: 15 March 2019

CONFIDENTIALITY STATEMENT

SPONSOR APPROVAL PAGE

Clinical Study Protocol Number: NSR-REP-01, Amendment 4.0, Version 5.0

Protocol Title: A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)

Protocol Date: 15 Mar 2019

Approved By: [redacted], MD

The person listed above is authorised to sign the protocol on behalf of NightstaRx Ltd. The wet-ink signature is on file and available upon request.

INVESTIGATOR'S SIGNATURE PAGE

Clinical Study Protocol Number: NSR-REP-01, Amendment 4.0, Version 5.0

Protocol Title: A Randomised, Open Label, Outcomes-Assessor Masked, Prospective, Parallel Controlled Group, Phase 3 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)

Protocol Date: 15 Mar 2019

I have read the Investigator's Brochure for AAV2-REP1 and I have read Protocol NSR-REP-01 and agree to conduct the study as outlined and in compliance with the Declaration of Helsinki (where required) and/or the International Council on Harmonization (ICH) guideline for Good Clinical Practice, and all applicable local and federal regulatory requirements and state/local laws. I agree to maintain confidentiality of my subjects and all information received or developed in relation to this protocol.

Signed: Date:

Name
Title
Institution
City, State (as applicable), Country

CONTACT INFORMATION

Role in Study	Name	Address	Telephone Number
Pharmacovigilance	[redacted]	[redacted] Email: [redacted]	[redacted]
Contract Research Organisation (CRO)	[redacted]	[redacted] UK [redacted] , UK	[redacted]

Further contact information is available in the Site Operations Manual.

Serious adverse events and Pregnancy Notification Forms should be emailed to [redacted]. For further information, refer to Section 12.3.

2 PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: NightstaRx, Ltd</td></tr>
<tr><td colspan="2">Name of Test Product: AAV2-REP1 (timrepigene emparvovec)</td></tr>
<tr><td colspan="2">Protocol Title: A Randomised, Open-Label, Outcomes-Assessor Masked, Prospective, Parallel-Controlled Group, Phase 3 Clinical Trial of Retinal Gene Therapy for Choroideremia Using an Adeno-Associated Viral Vector (AAV2) Encoding Rab Escort Protein 1 (REP1)</td></tr>
<tr><td colspan="2">Protocol Number: NSR-REP-01</td></tr>
<tr><td colspan="2">Study centres: The study will be conducted at approximately 20 study centres located in, but not limited to, North America and Europe.</td></tr>
<tr><td>Study period:
Screening, treatment and follow-up are approximately 14 months per subject</td><td>Phase of development: Phase 3</td></tr>
<tr><td colspan="2">Study Objective: The objective of the study is to evaluate the efficacy and safety of a single sub-retinal injection of AAV2-REP1 in subjects with choroideremia (CHM).</td></tr>
<tr><td colspan="2">Primary Endpoint: The primary efficacy endpoint is the proportion of subjects with a ≥15-letter improvement from Baseline in best corrected visual acuity (BCVA) at Month 12 as measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.
Key Secondary Efficacy Endpoints:
There are 3 key secondary efficacy endpoints:
1. Change from Baseline in BCVA at Month 12 measured by the ETDRS chart
2. Proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12 measured by the ETDRS chart
3. Proportion of subjects with no decrease from Baseline in BCVA or a decrease from Baseline in BCVA of <5 ETDRS letters at Month 12 in BCVA measured by the ETDRS chart
Other Secondary Endpoints:
• Change from Baseline in BCVA at Months 4 and 8
• Change from Baseline in total area of preserved autofluorescence (AF) at Month 12
• Change from Baseline in the area of preserved ellipsoid zone (spectral domain optical coherence tomography [SD-OCT]) at Month 12
• Change from Baseline in microperimetry at Month 12
• Change from Baseline in contrast sensitivity score at Month 12
• Change from Baseline in colour vision at Month 12
• Change from Baseline in reading speed test at Month 12
• Change from Baseline in the 25-item Visual Function Questionnaire (VFQ-25) at Month 12
Exploratory Efficacy Endpoint:
• [redacted]
Safety Endpoint:
• Evaluation of safety assessments, including adverse events (AEs), clinical laboratory assessments, vital signs</td></tr>
<tr><td colspan="2">Study Design: This is an outcomes-assessor-masked, prospective, randomised, parallel-controlled group, multi-centre, global, interventional study. The study consists of 8 visits with a 12-month evaluation period. During the Screening/Baseline period, each subject will be assessed for</td></tr>
</table>

eligibility. For eligible subjects, a study eye will be assigned, and the subjects will be randomised in a 2:1:2 ratio to receive either AAV2-REP1 high dose (1.0×10^11 genome particles [gp]), AAV2-REP1 low dose (1.0×10^10 gp) or to enter the untreated Control group.

On the Injection Day Visit (Visit 2, Day 0), subjects in the AAV2-REP1 high- and low-dose treatment arms will undergo vitrectomy and receive a sub-retinal injection of the assigned treatment dose of AAV2-REP1 in their study eye; these subjects will then return to the surgical site for 2 post-operative follow up visits on Day 1 (Visit 3) and, possibly for Day 7 (Visit 4; Day 7 can occur at either the surgical site or the home site depending on the clinical status of the subject). Subjects in the Control group will not undergo surgery, receive any study drug in their study eye (i.e., Control-study eye) or attend the 2 on-site post-operative visits. Instead, a telephone contact from the site will occur for the Control group on Day 0 (Visit 2), Day 1 (Visit 3) and Day 7 (± 3 days; Visit 4).

Day 0 (Visit 2) will be defined as the projected surgical day, whether the subject is randomised to treated or control groups.

All subjects will be followed for 12 months from Visit 2 (Day 0).

Study data will be collected for both eyes of each subject. Since AAV2-REP1 treatment requires an invasive surgical procedure under general anaesthesia, the sponsor, investigator and the subject will be unmasked to the study procedure (i.e., vitrectomy and sub-retinal injection), however within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^11 gp or 1.0×10^10 gp). To further minimise the potential bias of the treated and untreated eye evaluations, all subjective ophthalmic assessments from the Screening/Baseline Period (Visit 1) and from Month 1 (Visit 5) onwards (including the Month 12 Primary Endpoint evaluation) will be conducted by a masked assessor.

Subjects will be assessed for efficacy and safety throughout the study as indicated in the Schedule of Study Procedures. Subjects who develop cataracts may undergo cataract surgery if deemed clinically necessary; if surgery is performed, it should be carried out at least 4 weeks before the Month 12 Visit/End of Study (EOS) Visit.

Number of subjects (planned): Approximately 160 subjects randomised in a 2:1:2 ratio; 64 subjects in the AAV2-REP1 high dose (1.0×10^11 gp) group, 32 subjects in the AAV2-REP1 low dose (1.0×10^10 gp) and 64 subjects in the untreated control group.

Inclusion Criteria: Subjects are eligible for study participation if they meet all of the following inclusion criteria.

1. Are willing and able to give informed consent for participation in the study
2. Are male and ≥18 years of age
3. Have a documented genetically-confirmed diagnosis of CHM
4. Have active disease clinically visible within the macular region in the study eye
5. Have a BCVA of 34-73 ETDRS letters (equivalent to worse than or equal to 6/12 or 20/40 Snellen acuity, but better than or equal to 6/60 or 20/200 Snellen acuity) in the study eye.

Exclusion Criteria: Subjects are not eligible for study participation if they meet any of the following exclusion criteria.

1. Have a history of amblyopia in the eligible eye
2. Are unwilling to use barrier contraception methods, or abstain from sexual intercourse, for a period of 3 months, if treated with AAV2-REP1
3. Have had previous intraocular surgery performed in the study eye within 3 months of Visit 1
4. Have any significant ocular or non-ocular disease/disorder which, in the opinion of the investigator, may either put the subjects at risk because of participation in the study, or

may influence the results of the study, or the subject's ability to participate in the study. This includes but is not limited to, a subject:

a. with a contraindication to oral corticosteroid (e.g. prednisolone/prednisone)
b. with a clinically significant cataract
c. who, in the clinical opinion of the Investigator, is not an appropriate candidate for sub-retinal surgery

5. Have participated in another research study involving an investigational product in the past 12 weeks or received a gene/cell-based therapy at any time previously.

Test product, dosage, and mode of administration: All subjects receiving active treatment will undergo vitrectomy and receive a volume of up to 100 µL sub-retinally of either high dose (1.0×10^11 gp) AAV2-REP1 or low dose (1.0×10^10 gp) AAV2-REP1 in their study eye.

Reference therapy (Comparator), dosage, and mode of administration: The reference therapy in this study is no study medication/surgical procedure.

Criteria for Evaluation:

Efficacy: The efficacy evaluation will be based on BCVA, fundus AF, SD-OCT, microperimetry, contrast sensitivity, colour vision, reading speed test assessments, VFQ-25 and [redacted].

Safety: The safety evaluation will be based on full ophthalmic examination (including intraocular pressure, slit lamp examination, lens opacity grading, and dilated ophthalmoscopy), fundus photography, AE reporting, immunogenicity, and vital signs.

Any safety information collected as a result of the efficacy assessments (e.g., BCVA) will also be used in the overall safety evaluation, as appropriate.

Statistical Methodology:

Statistical tests will be performed at the alpha level of 0.05 (unless otherwise specified). Statistical tests and 95% confidence intervals (CIs) will be 2-sided.

Continuous variables will be summarised over time using descriptive statistics (i.e., mean, standard deviation, 95% CI, median, first and third quartiles, fifth and ninety-fifth percentiles, minimum, and maximum). Categorical variables will be described over time using counts, percentages, and 95% CIs.

The proportion of subjects with a ≥15-letter improvement from Baseline in BCVA at the Month 12 visit will be compared between study arms (high dose vs control, low dose vs control) using the Fisher's Exact test. The primary approach will be the unstratified analysis, and a supportive analysis will be conducted with the Cochran-Mantel-Haenszel approach by stratifying by Surgery Group. As Fisher's Exact test is overly conservative when the number of events is low, a supportive analysis will be conducted using Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001. To maintain the test at 0.05 two-sided level, the reported p-value will be 2 times the one-sided p-value from the Fisher's Exact-Boschloo test. The primary approach will be the unstratified analysis, and a supportive analysis will be conducted by stratifying by Surgery Group.

The primary analysis of the primary endpoint will be based on the ITT population, and a supportive analysis will be performed based on the PP population.

For continuous endpoints, point estimates and statistical comparisons will be generated based on an analysis of covariance (ANCOVA) model including Surgery Group, baseline value of the assessment, and study arms as covariates.

The protection of the type I error will be achieved for the comparison between the high dose and the untreated control under a hierarchical procedure. The primary efficacy endpoint will be first tested. If the p-value is <0.05, the study will be declared positive and the key secondary endpoints will be tested in the pre-specified order. The comparison between the low-dose arm and the

untreated control is considered as supportive, and will be performed only if significance is achieved between the high dose and the untreated control.

Adverse events will be summarised by system organ class, preferred term, and group. Both the number of eyes/subjects experiencing an AE and the number of events will be summarised. Similar summaries will be produced for study drug/procedure-related AEs, AEs leading to discontinuation, and serious adverse events (SAEs). AEs will also be summarised by maximum severity, relationship to study drug/procedure, and time to onset and resolution.

3 TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

LIST OF FIGURES

4 ABBREVIATIONS AND DEFINITIONS

Abbreviation or Term	Definition
AAV	adeno-associated virus
AAV2	AAV serotype 2
AAV2-REP1	AAV2 virus particle encapsulating 1.962kB cDNA of the wild-type human REP1 gene
AE	adverse event
AF	autofluorescence
ANCOVA	analysis of covariance
BCVA	best corrected visual acuity
BGH-polyA	bovine growth hormone polyadenylation
BSS	balanced salt solution
CBA	chicken β actin
(c)DNA	(complementary) deoxyribonucleic acid
CHM	choroideremia
CI	confidence interval
CRC	Central Reading Centre
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot
EOS	end of study
ET	early termination
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
gp	genome particle
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
IOP	intraocular pressure
IRB	Institutional Review Board
IReST	International Reading Speed Texts
[redacted]	[redacted]
LOCF	last observation carried forward
REP1	Rab escort protein 1
SAE	serious adverse event
SD-OCT	spectral domain optical coherence tomography
SUSAR	suspected, unexpected, serious adverse reaction
UK	United Kingdom
VA	visual acuity
VFQ-25	25-item Visual Function Questionnaire
WPRE	woodchuck hepatitis post-transcriptional regulatory element

5 INTRODUCTION

5.1 Choroideremia

Choroideremia (CHM) is a rare, untreatable retinal degeneration that begins in childhood with loss of night vision and gradually progresses to blindness by middle age. CHM is caused by loss of function of the gene encoding Rab escort protein 1 (REP1) which is located on the X-chromosome (Cremers 1990; Seabra 1993). The disease has an X-linked recessive mode of inheritance and affects approximately 1 in 50,000 people, mostly due to loss of function (null) mutations (Sankila 1992; MacDonald 2009).

5.2 Gene Therapy with Adeno-Associated Viral Vectors

Adeno-associated virus (AAV) is a parvovirus containing single stranded deoxyribonucleic acid (DNA). There are many different AAV subtypes, each with slightly different DNA sequences and capsid proteins. AAV serotype 2 (AAV2) is the vector to be used in this study. The wild type AAV2 genome lacks many of the viral sequences necessary for replication and packaging of viral particles and has evolved to become dependent on a helper virus (e.g. adenovirus or herpes simplex virus) for replication and spread from infected cells. In the absence of a helper virus, the AAV2 genome must remain dormant in the host cell which may have helped it to evolve to remain undetected by the eukaryotic immune system, although wild type AAV2 antibodies can be detected in about 30% of humans (Mingozzi 2007). Over time, the wild type AAV2 genome may become integrated into chromosome 19; however, this is not believed to occur in recombinant AAV because the integration mechanism involves part of the wild type sequence that is removed during cloning (Dutheil 2009).

The non-immunogenic features of AAV2 make it ideal for gene therapy. The principle is to remove the wild type AAV2 genome and replace it with a specific therapeutic transgene, thereby creating a “recombinant vector” which can deliver the therapeutic gene to diseased cells. The maximum size of the AAV2 genome is 4,700 base pairs and this must include the inverted terminal repeat sequences which remain at either end of the transgene (Lusby 1980). Hence the main drawback of AAV2 is the relatively small size of gene it can carry. At 1,900 base pairs however the REP1 complementary DNA (cDNA) coding sequence is well within this carrying capacity.

Gene therapy to the retina has advantages compared to other organs because the target area is small and much lower doses of vector can be applied by injection into the sub-retinal space, which is an enclosed natural anatomical compartment. Furthermore, the eye is a relatively immune-privileged organ which reduces further the degree of immune-mediated reactions to the AAV2 vector. AAV vectors target neurons effectively and AAV2 can infect rods, cones and the retinal pigment epithelium after sub-retinal injection in non-human primates (Jacobson 2006; Stieger 2006; Vandenberghe 2011). The retinal pigment epithelium is the cell layer that is primarily affected by the absence of REP1 in CHM, which correlates with the natural targeting of AAV2 delivered by sub-retinal injection. Hence, the AAV2 serotype is an ideal vector to treat this condition.

5.3 Study Rationale

CHM is a disease that causes blindness, with no available treatment option. The initial results from 6 patients included in a Phase 1/2 investigator-sponsored study (MacLaren 2014) show the investigational gene therapy medicinal product being generally well tolerated and

although the Phase 1/2 study was not powered to show efficacy, there were functional improvements in vision following retinal detachment and sub-retinal injection of AAV2-REP1 (0.6-1.0×10^10 genome particles [gp]), performed under general anaesthesia. In addition, long term maintenance of effect has been established for the 6 patients in the Phase 1 / 2 study for up to 4 years post treatment (Edwards 2016).

Three other open-label, single-dose, contralateral-control eye, Phase 2 investigator-sponsored studies were initiated and aimed to evaluate the effects of AAV2-REP1 over a 24-month period in adult male patients with a clinical and confirmed molecular diagnosis of CHM. The primary objective was to assess the safety and tolerability of AAV2-REP1. Across these studies, 18 patients (6 patients in each of the studies) have received 1.0×10^11 gp of AAV2-REP1 administered by sub-retinal injection into the macula following retinal detachment via vitrectomy. All studies utilised broadly the same protocol and trial design as the NSR-REP-01 study.

Additional data from the MacLaren study, including 8 patients treated with the high dose (1.0×10^11 gp) of AAV2-REP1, along with up to 48 months of efficacy results for the first 6 subjects who received the lower dose (1.0×10^10 gp), reveal encouraging efficacy and safety results. These data, together with up to 12 months of efficacy results for the 18 patients who received 1.0×10^11 gp of AAV2-REP1 in the Phase 2 trials (Dimopoulos 2018; Lam 2018; Xue 2018; Fischer 2018), reveal consistent findings with efficacy and safety, including no reported dose-limiting toxicities.

The initial results of these investigational retinal gene therapy trials are consistent with improved rod and cone function and overcome any negative effects of vitrectomy followed by retinal detachment induced during sub-retinal injection of vector. These findings demonstrate functional improvements in vision in a range of doses (1.0×10^11 gp and 1.0×10^10 gp) and lend support to the further assessment of AAV2-REP1 gene therapy in the treatment of CHM.

5.4 Benefit / Risk Assessment

No treatment currently exists for CHM.

The non-clinical studies conducted with AAV2-REP1 showed that it provides efficient and functional transgene expression in CHM mouse and human cells, as well as in mouse and human RPE and photoreceptors, without overt toxicity. Results from the 26-week single-dose combined toxicity/biodistribution study conducted in rats indicate that administration of AAV2-REP1 by single sub-retinal injection to both eyes is well tolerated at dose levels of 1×10^9 and 6×10^9 gp/eye (equal to 1×10^11 and 6×10^11 gp/eye in humans) when evaluated 4 and 26 weeks after injection. Minor reductions in some ERG parameters, ocular inflammation, and microscopic signs of retinal/corneal degeneration were observed and were considered procedure-related or not biologically significant.

In humans, application of AAV2-REP1 to the surface of the retina requires retinal detachment via vitrectomy. The 2-step procedure employed in delivering AAV2-REP1 sub-retinally (see Section 9.4), allows the management of unexpected surgical complications of retinal detachment before the AAV2-REP1 is applied. Furthermore, since the volume of fluid required to detach the fovea is variable, by excluding the vector from the first step, and administering the vector after successful retinal detachment has been achieved, a precise, consistent dose in terms of genome particles can be applied into the sub-retinal space.

Sub-retinal injection of AAV2-REP1 does carry the risks associated with vitrectomy and retinal detachment, which include intra-operative and post-operative complications; infection (most notably infectious endophthalmitis); low and elevated IOP; choroidal detachment; persistent retinal detachment, retinal tears, holes and breaks; macular hole and macular oedema; vitreous haemorrhage; visual impairment; metamorphopsia; and photopsia (Park 1995; Thompson 1996; Banker1997; Cheng 2001; Anderson 2006; Stein 009; Recchia 2010). Post-operative intraocular inflammation caused by vitrectomy is often associated with transient and sometimes permanent visual impairment. Another complication of vitrectomy is cataract formation, which may require an additional surgical procedure (cataract extraction) (Park 1995; Cheng 2001; Recchia 2010). In addition, the surgical procedure is performed under general anesthesia, which includes the risks of dizziness, confusion, nausea and vomiting.

Loss of visual acuity (VA) has been observed post-treatment with AAV2-REP1. This VA loss was determined by investigators to be plausibly related to the administration of AAV2-REP1, however without definitively attributing the cause to either the study procedure or the GTMP. Loss of VA is, therefore, considered a Potential Risk of AAV2-REP1 treatment, in addition to the above-described potential and anticipated surgical risks. See the Investigator's Brochure for AAV2-REP1 for further details.

Thus, although there are risks associated with the administration of the study treatment via vitrectomy and retinal detachment, the potential for benefit in the form of improved VA potentially provided to subjects with CHM following treatment with AAV2-REP1 provides an acceptable benefit-risk profile for participation in this study.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Objective

The objective of the study is to evaluate the efficacy and safety of a single sub-retinal injection of AAV2-REP1 in subjects with CHM.

6.2 Endpoints

6.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects with a ≥15-letter improvement from Baseline in best corrected visual acuity (BCVA) at Month 12 as measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

6.2.2 Key Secondary Efficacy Endpoints

There are 3 key secondary efficacy endpoints:

1. Change from Baseline in BCVA at Month 12 measured by the ETDRS chart
2. Proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12 measured by the ETDRS chart
3. Proportion of subjects with no decrease from Baseline in BCVA or a decrease from Baseline in BCVA of <5 ETDRS letters at Month 12 measured by the EDRS chart

6.2.3 Other Secondary Endpoints

- Change from Baseline in BCVA at Months 4 and 8
- Change from Baseline in total area of preserved autofluorescence (AF) at Month 12
- Change from Baseline in the area of preserved ellipsoid zone (spectral domain optical coherence tomography [SD-OCT]SD-OCT) at Month 12
- Change from Baseline in microperimetry at Month 12
- Change from Baseline in contrast sensitivity score at Month 12
- Change from Baseline in colour vision at Month 12
- Change from Baseline in reading speed test at Month 12
- Change from Baseline in the 25-item Visual Function Questionnaire (VFQ-25) at Month 12

6.2.4 Exploratory Efficacy Endpoints

[redacted]

6.2.5 Safety Endpoints

The safety endpoints are:

- Overall adverse events (AEs), serious AEs (SAEs), and AEs (or SAEs) leading to discontinuations

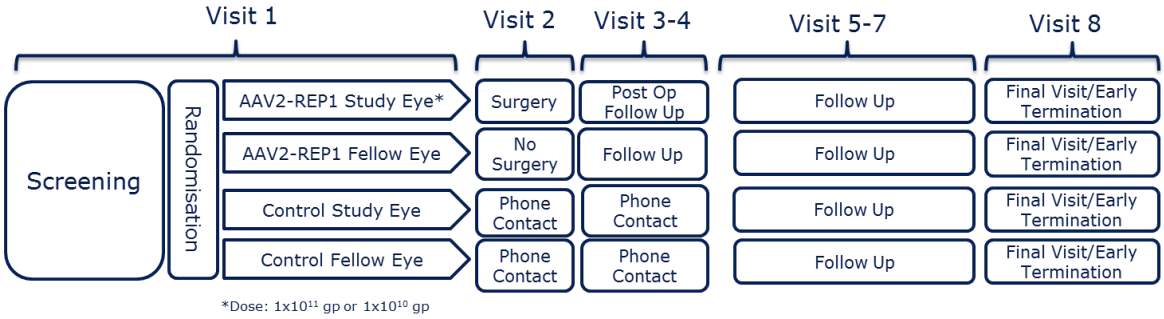
- Clinical laboratory evaluations
- Vital signs including diastolic blood pressure, systolic blood pressure, and pulse

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This is an outcomes-assessor-masked, prospective, randomised, parallel-controlled group, multi-centre, global, interventional Phase 3 study, consisting of 8 visits with a 12-month evaluation period. A study schematic is presented below.

Figure 1 Overall Study Schematic



During the Screening/Baseline period (Visit 1), each subject will be assessed for eligibility. If a subject has only 1 eligible eye, that eye will be designated as the "study eye" and the subject's other (non-eligible) eye will be designated as the "fellow eye." If a subject has 2 eligible eyes, the selection of the "study eye" will be made on clinical grounds and will generally be the worse eye affected. This will be discussed in detail and agreed with each subject as part of the informed consent process. Subject choice will be considered in cases where the degeneration is relatively symmetrical between the two eyes.

During the Screening/Baseline period, eligible subjects will be randomised in a 2:1:2 ratio to either the AAV2-REP1 high-dose group (1.0×10^11 gp), the AAV2-REP1 low-dose group (1.0×10^10 gp) or the untreated Control group. To facilitate understanding of the study design, eyes will be classified into 4 categories based on treatment-group assignment and designation of study/fellow eye: AAV2-REP1-study eye (includes high and low dose); AAV2-REP1-fellow eye (includes high and low dose); Control-study eye; and Control-fellow eye. Once a subject has been randomised, a change in "study eye" designation is not permitted.

At the time of randomisation, a projected surgical date should be defined for each subject. For each subject randomised to the control group, this projected surgical date (+/- 1 day) should remain the Day 0 (Visit 2) date. For each subject randomised to a treated group, Day 0 (Visit 2) will be the actual date of surgery. The Screening / Baseline period must occur within 8 weeks prior to dosing (Week 2, Day 0).

On this visit (Visit 2, Day 0), subjects in the AAV2-REP1-treatment groups will undergo vitrectomy and retinal detachment before receiving a sub-retinal injection of AAV2-REP1 high dose (1.0×10^11 gp), or AAV2-REP1 low dose (1.0×10^10 gp) in their study eye (i.e., AAV2-REP1-study eye).

These treated subjects will then return to the site for 2 post-operative follow up visits on Day 1 (Visit 3) and, possibly, Day 7 (Visit 4; Day 7 can occur either at the surgical site or the host site, depending on the clinical status of the subject). Subjects in the Control group will not undergo surgery, receive study drug or attend the 2 on-site safety post-operative visits.

Instead, a telephone contact from the site will occur for the Control group on Day 0 (Visit 2), Day 1 (Visit 3) and Day 7 (± 3 days; Visit 4).

All subjects will be followed for 12 months from Visit 2 (Day 0). Study data will be collected for both eyes of each subject.

Since AAV2-REP1 treatment requires an invasive surgical procedure under general anaesthesia, the sponsor, investigator and the subject will be unmasked to the study procedure (i.e. vitrectomy and sub-retinal injection), however within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^11 gp or 1.0×10^10 gp). To further minimise the potential bias of the treated and untreated eye evaluations, all subjective ophthalmic assessments from the Screening/Baseline period (Visit 1) and from Month 1 (Visit 5) onwards, will be conducted by a masked assessor. Subjects will be assessed for efficacy and safety throughout the study as indicated in the Schedule of Study Procedures (see Section 17.1).

The efficacy evaluation will be based on BCVA, fundus AF, SD-OCT, microperimetry, contrast sensitivity, colour vision, reading speed test, VFQ-25 [redacted]. The safety evaluation will be based on full ophthalmic examination (including IOP, slit lamp examination, lens opacity grading, and dilated ophthalmoscopy), fundus photography, adverse event (AE) reporting, laboratory assessments (immunogenicity), and vital signs. Any safety information collected as a result of the efficacy assessments (e.g., BCVA) will also be used in the overall safety evaluation, as appropriate.

Subjects who develop cataracts may undergo cataract surgery if deemed clinically necessary; if surgery is performed, it should be carried out at least 4 weeks before the Month 12 Visit/End of Study (EOS) Visit (primary endpoint).

A subject is considered to have completed the study if he completes the Month 12 assessments. The end of the trial is the date the last subject completes his Month 12 assessments (or early termination [ET] assessments in the event of premature discontinuation) or the date of last data collection if the last subject is lost to follow-up. After study completion, treated subjects will be invited to participate in a long term follow up study which will permit continued efficacy and safety monitoring over a period of 5 years post-treatment.

7.2 Discussion of Design

The subjects to be included in the study are representative of active CHM disease and are being selected in such a way as to optimise observance of meaningful change in the outcome measures (i.e., baseline BCVA 34-73 ETDRS letters avoids potential ceiling/floor effects for change from baseline BCVA measures). The planned sample size (approximately 160 subjects) is considered to be a comprehensive number of subjects considering the rarity of the disease and provides adequate power to observe the expected treatment effect (see Section 13.1 for details). A prospective trial period of up to 12 months for efficacy and safety is considered a sufficient period of time to observe clinically relevant changes in disease status among subjects selected for the study and to assess the safety of the investigational drug. In the AAV2-REP1 Investigator-Sponsored trials, efficacy has been observed as early as Month 1, with stabilisation of efficacy at Month 3 onwards in responders (patients with ≥ 15 letter gains versus baseline).

The choice of control for this parallel-group study is no study medication/surgical procedure. Since administration of vector requires vitrectomy, an invasive surgical procedure under general anaesthesia, a similar sham treatment procedure was not ethically feasible. A

parallel-group design was selected following feedback from regulatory authorities. The choice of primary endpoint (proportion of patients with ≥ 15-letter gain) is well-accepted as a clinically meaningful improvement in visual function (Csaky 2017).

The sponsor, investigator and subject will be unmasked to the study procedure and treatment (i.e. vitrectomy and sub-retinal injection). However, within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^11 gp or 1.0×10^10 gp). To further minimise potential bias of the treated and non-treated eye evaluations, all subjective ophthalmic assessments collected during the Screening/Baseline period (Visit 1) and from Month 1 (Visit 5) onwards will be conducted by a masked assessor.

The dose range of vector being employed in this study is based on previous clinical trials using the AAV2 vector with a chicken β actin (CBA) promoter (Maguire 2009; MacLaren 2014) and investigator-driven clinical studies in which AAV2-REP1 was administered to subjects with CHM (MacLaren 2014; Dimopoulos 2018; Lam 2018; Xue 2018). Efficacy has been observed in doses of 1.0×10^10 gp or 1.0×10^11 gp in these Investigator-Sponsored trials, with approximately 17% of patients in the target population treated with 1.0×10^11 gp achieving ≥ 15 letter improvement at 12 months post-treatment. The high dose of 1.0×10^11 gp is planned to be administered in this study at a higher allocation ratio than the lower dose of 1.0×10^10 gp because the high dose provides optimal multiplicity of infection ratios, has been previously tested in the Investigator-Sponsored trials and has been generally well tolerated thus far. In addition, randomisation is stratified by surgical group, to account for potential confounders (e.g., differences in care provided according to country/region).

Application of AAV2-REP1 to the retina requires retinal detachment following vitrectomy. To improve visualization of the vector and facilitate dosing, surgeons are given the option of adding a minute quantity of trypan blue ophthalmic solution (~6 µL) to the vector solution. See the AAV2-REP1 Surgical Manual for further details.

Sub-retinal injection of AAV2-REP1 carries the risks associated with vitrectomy and retinal detachment. These and other surgical risks are discussed in Section 5.4. To minimise inflammation resulting from potential immune responses to vector, subjects receiving AAV2-REP1 will be given a course of oral corticosteroid (e.g., prednisolone / prednisone) (see Section 9.8 for details).

8 SELECTION AND WITHDRAWAL OF SUBJECTS

The study will enroll approximately 160 subjects with CHM (see Section 13.1 for discussion of the sample size determination). The majority of patients enrolled in this study will be from the preceding NIGHT observational study (Protocol NSR-CHM-OS1).

8.1 Inclusion Criteria

Subjects are eligible for study participation if they meet all of the following inclusion criteria.

1. Are willing and able to provide informed consent for participation in the study
2. Are male and ≥18 years of age
3. Have a documented genetically-confirmed diagnosis of CHM
4. Have active disease clinically visible within the macular region in the study eye
5. Have a BCVA of 34-73 ETDRS letters (equivalent to worse than or equal to 6/12 or 20/40 Snellen acuity, but better than or equal to 6/60 or 20/200 Snellen acuity) in the study eye

8.2 Exclusion Criteria

Subjects are not eligible for study participation if they meet any of the following exclusion criteria.

1. Have a history of amblyopia in the eligible eye
2. Are unwilling to use barrier contraception methods, or abstain from sexual intercourse, for a period of 3 months, if treated with AAV2-REP1
3. Have had previous intraocular surgery performed in the study eye within 3 months of Visit 1
4. Have any significant ocular or non-ocular disease/disorder which, in the opinion of the investigator, may either put the subjects at risk because of participation in the study, or may influence the results of the study, or the subject's ability to participate in the study. This includes but is not limited to, a subject:
    - with a contraindication to oral corticosteroid (e.g., prednisolone/prednisone)
    - with a clinically significant cataract
    - who, in the clinical opinion of the Investigator, is not an appropriate candidate for sub-retinal surgery
5. Have participated in another research study involving an investigational product in the past 12 weeks or received a gene/cell-based therapy at any time previously

8.3 Subject Withdrawal Criteria

Each subject has the right to withdraw from the study at any time without prejudice. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including:

- Significant protocol deviation
- Significant non-compliance with study requirements

- AE which results in an inability to continue to comply with study assessments
- Lost to follow up
- Death
- Other (to be specified on the electronic case report form [eCRF]).

In the event that a subject discontinues the study, the reason for withdrawal is to be recorded in the eCRF. In the event that a subject discontinues the study early, the site should use every reasonable effort to ensure that an ET Visit is conducted as outlined in the Schedule of Study Procedures (see Section 17.1). If the subject is withdrawn due to an AE, the investigator will arrange for follow-up until the event has resolved or stabilised. For subjects who withdraw consent, data will be collected through their last available study visit. Subjects withdrawn from the study may possibly be replaced.

Withdrawal from the study will not result in the exclusion of a subject's data acquired up to the point of withdrawal.

The study may be discontinued if the Sponsor deems it necessary for medical, safety, regulatory, business or other reasons consistent with applicable or regulations.

9 STUDY TREATMENT

9.1 Treatments Administered

During the Screening/Baseline period, eligible subjects will be randomised in a 2:1:2 ratio to receive either AAV2-REP1 high dose (1.0×10^11 gp), AAV2-REP1 low dose (1.0×10^10 gp) or to enter the untreated Control group. The "study eye" must be selected prior to randomisation. Once a subject has been randomised, a change in "study eye" designation is not permitted.

At the time of randomisation, a projected surgical date should be defined for each subject. For each subject randomised to the control group, this projected surgical date (+/- 1 day) should remain the Day 0 (Visit 2) date. For each subject randomised to a treated group, Day 0 will be the actual date of surgery.

For those randomized to treated groups, at this visit (Visit 2, Day 0), subjects will be administered AAV2-REP1 as a sub-retinal injection after vitrectomy (See Section 9.4 for details). Subjects in the untreated Control group will receive no sham surgery or study medication.

9.2 Description of Study Drug

The AAV2 vector contains recombinant human cDNA encoding REP1 (AAV2-REP1). The vector genome (AAV2-CBA-hREP1-WPRE-BGH) is comprised of a strong constitutive expression cassette, a hybrid CBA promoter, the human cDNA encoding REP1, a modified woodchuck hepatitis post-transcriptional regulatory element (WPRE) sequence, and a bovine growth hormone polyadenylation (BGH-polyA) sequence flanked by AAV2 inverted terminal repeats. The cDNA fragment was originally isolated from a human retinal cDNA library from unaffected individuals.

The AAV2-REP1 drug product is formulated in a sterile, 20 mM Tris-buffered solution, pH 8.0, and contains 1 mM $MgCl_2$, 200 mM NaCl, and 0.001% PF68. The drug product is a clear to slightly opalescent, colourless, sterile-filtered suspension with a target concentration of 1.0 × 10^12 gp/mL.

9.3 Packaging, Labelling, and Storage

AAV2-REP1 is currently supplied in sterile, single-use, clear glass or plastic vials, stoppered, and capped with plastic overseals, with each vial containing 300 µL vector suspension. Each vial contains 3.0×10^11 gp in total. Prior to shipment, each vial will be placed in a labeled secondary container. The drug product is to be stored at <−60ºC (<−76ºF) in a controlled access, temperature monitored freezer.

The Investigational Medicinal Product will be labeled in compliance with regulatory standards.

9.4 Vitrectomy Procedure and Injection of AAV2-REP1

Injection of AAV2-REP1 is to be performed by an appropriately qualified and experienced retinal surgeon. All surgeons must have completed all study-specific surgical training and obtained certification by NightstaRx to perform the study procedure, before treating a study participant.

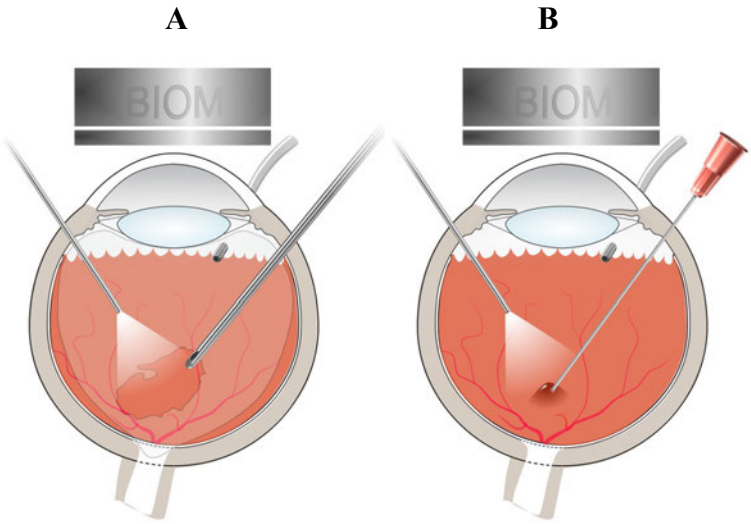
Due to the complexity and unpredictability of detaching the retina in end-stage CHM, in which the retina and choroid are extremely thin and fused in places, a modification to the technique of sub-retinal gene therapy has been developed. This involves performing the vector delivery in 2 steps after vitrectomy. An advantage of a 2-step procedure is that any unexpected complications of retinal detachment can be managed conservatively, minimising concerns about the vector escaping into the vitreous. Further, the injection could be deferred until a later date if, for instance, a macular hole was created which required treatment with gas. Also, since the volume of fluid required to detach the fovea is variable, by removing the vector from the first step, a precise consistent dose in terms of genome particles can still be applied into the sub-retinal space.

Initially, subjects will undergo a standard vitrectomy and detachment of the posterior hyaloid (Figure 2). All surgery will be conducted using the standard BIOM vitrectomy system. A 23-gauge sutured approach is usually favoured to avoid any potential risks of wound leakage. The retina will be detached with 100-500 µL of balanced salt solution (BSS) injected through a 41-gauge sub-retinal cannula connected to a vitreous injection set (this is the first step of the 2-step procedure).

In the second step of the procedure, the BSS cannula is removed from the eye and AAV2-REP1 is prepared for injection. The dilution process for the 1.0×10^10 gp dose is outlined in the Pharmacy Manual. A dose of either 1.0×10^11 or 1.0×10^10 AAV2-REP1 gp (injection of a volume of up to 100 µL vector suspension) will be injected into the sub-retinal fluid through the same entry site. To improve visualization of the vector and facilitate dosing, surgeons are given the option of adding a minute quantity of trypan blue ophthalmic solution (~6 µL) to the vector solution. See the AAV2-REP1 Surgical Manual for further details (see Figure 2). The vector needs to be primed in the 1-mL syringe to avoid formation of air bubbles, and a connector is used so that the 1-mL syringe can be connected to the constant pressure line of the vitrectomy machine. The sub-retinal injection will target any area of the macula but also include the fovea, if possible. In each case, the vector will be injected so that the sub-retinal fluid overlies all edge boundaries of the central region that has yet to undergo chorioretinal degeneration, as identified by fundus AF. After wound closure, care will be taken to dispose of all irrigating fluids that may have passed through the eye to limit potential vector spread.

Subjects will be carefully monitored for the occurrence of AEs peri- and post-operatively. All AEs, irrespective of relationship to the study drug and/or the surgical procedure will be captured in the subject's medical record and reported in the eCRF.

Figure 2 Vitrectomy and Sub-retinal Injection of AAV2 Vector



(A) A standard vitrectomy through the BIOM operating system to remove the vitreous gel is followed by (B) 2-step procedure: 1) retinal detachment by injection of BSS; 2) injection of a volume of up to 100 µL vector suspension through a 41-gauge cannula into the sub-retinal space.

9.5 Randomisation

During the Screening/Baseline period, all subjects will be assigned a screening identifier, which will include the centre number and subject number. If the subject fulfils all eligibility criteria during the Screening/Baseline period, a study eye will be assigned (prior to randomisation) and the subject will be randomised in a 2:1:2 ratio to receive either AAV2-REP1 high dose (1.0×10^11 gp), AAV2-REP1 low dose (1.0×10^10 gp) or to enter the untreated Control group.

Randomisation will be generated using a validated system that automates the random assignment of treatment groups, and stratified by surgical group*. Once a subject is deemed eligible, the investigative site (or authorised designee) will access the system, and the subject will be randomised using a standard blocked randomisation.

Once a subject has been randomised, a change in "study eye" designation is not permitted.

At the time of randomisation, a projected surgical date should be defined for each subject. For each subject randomised to the control group, this projected surgical date (+/- 1 day) should remain the Day 0 (Visit 2) date. For each subject randomised to a treated group, Day 0 will be the actual date of surgery.

All subjects' data (including screen failures) will be entered into the eCRF.

* A surgical group will consist of a single 'Surgical Site' and 'Non-surgical Sites'. The Surgical Site will conduct baseline and follow-up visits for local subjects, as well as surgeries and immediate post-operative visits for all subjects treated in the surgical group. The 'Non-surgical Sites' will only perform the baseline/screening visit and the follow-up visits from Day 7 (Visit 4) onwards for their respective local subjects.

9.6 Study Masking and Minimisation of Bias

Randomisation of subjects aims to minimise potential selection bias.

Given a double-masked design is not feasible (i.e. treatment involves invasive surgical procedure under general anaesthesia), the sponsor, investigator and the subject will be

unmasked to whether a subject has been assigned to the AAV2-REP1 treatment groups, or the untreated Control group. However, within the treated groups, the sponsor, investigator and subject will be masked to the assigned dose (1.0×10^11 gp or 1.0×10^10 gp). To further minimise potential performance/detection bias, all subjective ophthalmic assessments at the Screening/Baseline Period (Visit 1) and from Month 1 (Visit 5) onwards, will be conducted by a masked (outcomes) assessor.

Additional measures to minimise potential performance/detection bias include standardised methodologies across participating sites (same equipment, assessor training/certification, surgical training), and an identical visit/assessment schedule for treated/untreated patients.

9.6.1 AAV2-REP1 Treatment Groups vs Untreated Control Group, Assessor Masking

All ophthalmic assessments conducted during the Screening/Baseline period will be performed by appropriately qualified masked assessors. For the immediate post-operative visits, masking of the assessors will not be viable as clinical signs of surgery will be apparent (i.e. redness, swelling). Therefore, unmasked assessors will perform all ophthalmic assessments at Visit 3 (Day 1) and Visit 4 (Day 7). From Visit 5 (Month 1) onwards, masked assessors will be used, as any signs of surgery will have dissipated and it will not be possible clinically to differentiate between those subjects that have not undergone surgery, and those subjects that have undergone surgery and received active treatment.

Subjects randomised to the untreated Control group will not be required to attend the site at Visit 2, 3 or 4. As the key purpose of Visit 2 is surgery, and Visit 3 and 4, post-operative safety, there is limited utility in Control subjects attending. This will also limit the study burden for Control subjects, thereby potentially reducing the risk of subject withdrawal at this stage, and reducing the possibility of further unmasking due to direct contact and communication with fellow participants. Instead, a telephone contact from the site will occur for the Control group on Day 0 (Visit 2), Day 1 (Visit 3) and Day 7 (± 3 days; Visit 4).

In order to minimise bias further, masked assessors will not have access to the subject's medical records, source documentation or eCRF as data entries or notation (such as use of peri-operative corticosteroid) may be sources of unmasking. From Visit 5 (Month 1) onwards, the masked assessor will also read a pre-written statement to each subject, regardless of randomisation, reminding them of the masked nature of the study, and to avoid any reference to prior surgery/non-surgery, which eye may have received treatment or to allude to any information that may unmask the assessor as to which group the subject has been assigned to.

Furthermore, it is anticipated that a subset of the subjects participating in the trial will be active on social media. Following appropriate approval by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), the patient information leaflet will request that subjects refrain from posting any details of study participation on social media, that may unmask the assessors to the group the subject has been assigned to. This request will be reiterated at visits by the investigator and within the pre-written statement.

Table 1 describes the ophthalmic assessments that are to be performed by masked assessors at Screening/Baseline (Visit 1) and Visits 5-8.

Table 1 Assessor Masked Ophthalmic Assessments

Assessment	Masked Outcomes Assessors at Visit 1 and Visits 5-8
BCVA	✓
Microperimetry	✓
Contrast Sensitivity	✓
[redacted]	
Colour Vision	✓
Reading Speed	✓
VFQ-25	✓

Abbreviations: BCVA= best corrected visual acuity, [redacted], VFQ-25=25-item Visual Function Questionnaire

9.6.2 AAV2-REP1 Treatment Groups, Dose Masking

Subjects randomised to the AAV2-REP1 treatment groups, surgeons, the investigative team and the study sponsor will be masked as to which dose of AAV2-REP1 the subject has been assigned to. All vector vials will be filled at 1.0 × 10^11 gp. Therefore, for subjects who are due to receive the lower dose of 1.0 × 10^10 gp, a dilution step is required prior to surgery. Unmasked study site personnel will be assigned the responsibility of performing the dilution in accordance with the Pharmacy manual, in a designated area remote from the investigative team to preserve masking of the treatment arm. Personnel delegated to perform the dilution will not be involved in any other aspect of the study (i.e., consent, safety/efficacy assessments, surgical procedure).

9.7 Study Drug Accountability

Records of the receipt and dispensing of study drug, which should include the diluent if used, will be kept by each study centre until the end of the study to provide complete accounting of all used and unused study drug. Dispensation logs will be checked by the Sponsor (or its designee). Study centres will destroy all used vials in accordance with local procedures, and will return all unused study drug to the Sponsor (or its designee) at the end of the study. Final drug accountability will be verified by the Sponsor (or its designee).

9.8 Concomitant Therapy

Subjects cannot have participated in another research study involving an investigational product in the past 12 weeks or received a gene/cell-based therapy at any time previously.

Throughout the study, subjects may be prescribed any concomitant medications, procedures, and/or treatments deemed necessary. Details of concomitant medications, procedures, and treatments will be collected at the Screening/Baseline Visit and updated at every study visit (including the ET Visit, if applicable). Concomitant medications, procedures and treatments (including corticosteroids) taken during the study are to be recorded in the subject's medical records and eCRF; an exception to this is any medication used in the course of conducting a study assessment (e.g., ophthalmic dyes, topical anaesthesia, dilating eye drops).

To minimise inflammation resulting from surgery and potential or unexpected immune responses to vector/transgene, all subjects who receive AAV2-REP1 will be given a 21-day course of oral corticosteroid (e.g., prednisolone/prednisone), modified from the 17-day protocol established in the voretigene neparvovec-rzyl AAV gene therapy clinical trial for treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy (Maguire 2008), allowing an extra 4 days for tapering the dose at the end of the course. Hence, this will be 1 mg/kg/day prednisolone/prednisone for a total of 10 days, (beginning 2 days before the vector injection, on the day of injection, and then for 7 days), followed by 0.5 mg/kg/day for 7 days, then 0.25 mg/kg/day for 2 days and 0.125 mg/kg/day for 2 days (21 days in total). Weight captured at Visit 1 (Screening/Baseline) will be used to calculate the required dose during the 21-day course, and all doses should be rounded to the nearest 1 mg. Compliance with the use of corticosteroid (e.g., prednisolone / prednisone) will be captured in a patient diary card and in the eCRF.

9.9 Treatment Compliance

This study involves a single sub-retinal injection of a volume of up to 100 µL AAV2-REP1 containing either 1×10^11 gp or 1×10^10 gp following vitrectomy by a qualified retinal surgeon. The exact quantity injected at the time of surgery should be recorded on the eCRF. Measure of treatment compliance with AAV2-REP1 is therefore not necessary.

10 STUDY VISITS AND PROCEDURES

The schedule of study procedures is presented in Table 3.

10.1 Visit 1 (Screening/Baseline Period)

The investigator will explain the study purpose, procedures, and subject responsibilities to each potential study subject. The subject's willingness and ability to meet the protocol requirements will be determined.

Prior to any study-specific procedure, written informed consent will be obtained. The subject will sign and date one copy of the consent form in the presence of the investigator or his/her designee. The original signed form will be retained at the study site and an additional copy will remain in the subject's medical records; a copy will also be given to the subject. The informed consent must be signed within 12 weeks prior to the treatment visit (Visit 2, Day 0).

After informed consent has been obtained, the subject will be allocated a subject identifier number and evaluated to determine eligibility. The Screening / Baseline Period (Visit 1) must be completed within 8 weeks prior to the treatment visit (Visit 2, Day 0).

Subjects randomised to the AAV2-REP1 groups will be instructed to use barrier contraception, or abstain from sexual intercourse, for a period of 3 months from the time they are treated.

In some cases, subjects randomised to receive AAV2-REP1 will travel to alternative qualified investigative sites to undergo the study surgical procedure, and then return back to the original (host) investigational site for study follow up. The post-operative visits at Day 1 (Visit 3) and possibly at Day 7±3 Days (Visit 4) will occur at the surgical site, while the remaining visits will occur at the original, host site. The Sponsor will provide the investigational sites, subject and any appropriate caregiver with necessary logistical support, with arrangements made for Visits 2, 3 and 4 to allow for adequate planning and post-operative follow-up.

If the subject is randomised to the Control group, then Visit 2 will consist of a telephone call (see Section 10.2).

For subjects who roll over from the observational NIGHT study (Protocol NSR-CHM-OS1) into this interventional study, the assessments and procedures conducted at the final visit (including the ET Visit) of the NIGHT study may be used for the Screening/Baseline Visit in the current study, as long as the visit occurred within 8 weeks of Visit 2 (dosing).

If the subject was not previously enrolled in the NIGHT study, BCVA assessments at baseline must be performed in triplicate over a period of 2 days, as described above. At least 2 of the triplicate values must meet BCVA eligibility requirements for inclusion in the study, and the difference between the 3 assessments may not be ≥ 10 letters.

Screening/baseline procedures will consist of the following (assessments can be spread over 2 consecutive days if necessary):

- Demography, medical and ocular history. (Only subjects with a genetically confirmed diagnosis of CHM may enter the study. Genetic confirmation must be documented prior to Visit 1)
- VFQ-25[1]
- Vital signs

- Weight
- Immunoassay sampling (enzyme-linked immunosorbent assay [ELISA], cell-based assay, and enzyme-linked immunospot [ELISPOT])
- [redacted]
- BCVA[3]
- Contrast sensitivity test
- Colour vision test
- Reading speed test[4]
- Microperimetry
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- 7-field colour fundus photography (including stereo photographs for fields 1, 2, and 3)
- Adverse event (AE) and serious adverse event (SAE) monitoring
- Concomitant medication, procedures, and treatment review
- Corticosteroid dispensing (if randomised to AAV2-REP1 groups)

  Subjects randomised to the AAV2-REP1 groups will be given a 21-day course of oral corticosteroid (e.g., prednisolone/prednisone) and instructed to start taking the drug 2 days before their next study visit (Visit 2).

- Randomisation

  Subjects who meet all of the inclusion criteria and none of the exclusion criteria will have a study eye assigned and be enrolled into the study (see Section 9.5 for details on randomisation and assignment of subject numbers). At this time, subjects will be informed of the randomisation outcome (i.e., AAV2-REP1 treatment or the Control group) and instructed to not reveal their treatment group assignment to the masked assessors during the study. Subjects randomised to the AAV2-REP1 treatment groups (along with the Investigators and sponsor) will remain masked to the assigned dose.

  At the time of randomisation, a projected surgical date should be defined for each subject. For each subject randomised to the control group, this projected surgical date (+/- 1 day) should remain the Day 0 (Visit 2) date. For each subject randomised to a treated group, Day 0 will be the actual date of surgery.

  Once a subject has been randomised, a change in "study eye" designation is not permitted.

1. VFQ-25 must be completed by subjects at the beginning of the study visit, prior to any significant interaction with study staff; the questionnaire is used only in languages in which it is validated.

[redacted]

3. In order to capture accurate BCVA values at Visit 1 (Screening/Baseline), the following conditions apply to the BCVA assessment:

- If the BCVA value at Visit 1 (Screening/Baseline) is ≥ ±10 letter gain or loss in the study eye compared to the previous NIGHT study visit (if applicable), then BCVA must be repeated an additional 2 times, resulting in a total of 3 BCVA measures at Visit 1. To facilitate the additional BCVA measures this visit should be conducted over 2 days, with BCVA measured twice on Day 1 and once on Day 2. All 3 BCVA values must be recorded in the eCRF. The highest score will be used to define subject eligibility.
- If the BCVA value at Visit 1 (Screening/Baseline) is < ± 10-letter difference in the study eye compared to the previous NIGHT study visit (if applicable), then BCVA will be collected once and will not be repeated.

If the subject was not previously in the NIGHT study, BCVA assessments at baseline must be performed in triplicate over a period of 2 days, as described above. At least 2 of the triplicate values must meet BCVA eligibility requirements for inclusion in the study and the difference between the 3 assessments may not be greater than or equal to 10 letters.4. The International Reading Speed Texts (IReST) speed reading test is only conducted in languages in which a validated translation is available.

10.2 Visit 2 (Day 0, Injection Day Visit or Telephone Contact)

At Visit 2 (Day 0), all subjects in the AAV2-REP1-treated groups will visit the surgical site, and the following assessments will be performed:

- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review
- Corticosteroid compliance review

It may be necessary for subjects to undergo a pre-surgical workup according to local hospital procedures (e.g., blood draw for anesthetist) which are outside of the protocol-defined assessments. Any assessments performed outside of the protocol will not be collected as part of the study analyses.

Subjects in the AAV2-REP1-treated groups will then undergo vitrectomy and receive a sub-retinal injection of AAV2-REP1, containing either 1×10^11 gp or 1×10^10 gp (see Section 9.4 for details), in their study eye. Subjects will be carefully monitored for the occurrence of AEs during and after the procedure.

Subjects will return to the surgical site for Visit 3 (post-operative Day 1). Visit 4, post-operative Day 7, may occur at the surgical site or the host site depending on the clinical status of the subject.

Subjects in the Control group will receive the Visit 2 (Day 0) Telephone Call at the agreed upon date and time. Sites will conduct the following assessments during the telephone call:

- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

10.3 Visit 3 (Day 1 Post-Operative Visit)

At Visit 3 (Day 1), subjects in the AAV2-REP1 groups will return to the surgical site for a post-operative visit. The following assessments will be performed:

- Vital signs

- Immunoassay sampling (ELISA and cell-based assays only)
- BCVA
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review
- Corticosteroid compliance review

Subjects will be reminded of the requirement to use barrier contraception for a period of 3 months from the time of treatment.

Subjects in the Control group will receive the Visit 3 Telephone Call at the agreed upon date and time. Sites will conduct the following assessments during the telephone call:

- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

10.4 Visit 4 (Day 7 Post-Operative Visit ± 3 Days)

At Visit 4 (Day 7 ± 3 days), subjects in the AAV2-REP1 groups will return for a second post-operative assessment.

For subjects who traveled from a host site (i.e. same site where their Visit 1 Screening/Baseline visit was performed) to a surgical site for their surgical procedure, this visit may occur either at the surgical site or the host site. However, in the event of a post-operative complication or for any other safety reason considered appropriate by the study surgeon and surgical site Investigator, Visit 4 should be conducted at the surgical site. In this case, post-operative follow-up should continue at the surgical site until the surgeon/surgical site Investigator agrees to discharge the subject to the care of the non-surgical site.

The following assessments will be performed:

- Vital signs
- Immunoassay sampling
- [redacted]
- BCVA
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review
- Corticosteroid compliance review

Subjects in the Control group will receive the Visit 4 Telephone Call at the agreed upon date and time (± 3 days of Day 7). Sites will conduct the following assessments during the telephone call:

- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

10.5 Visit 5 (Month 1 ± 7 Days)

All subjects, regardless of treatment randomisation, will attend their host site (i.e. same site where their Visit 1 Screening/Baseline visit was performed) from Visit 5 onwards. At Visit 5 (Month 1 ± 7 days), the following assessments will be performed for all subjects (assessments can be spread over 2 consecutive days if necessary):

- Vital signs
- Immunoassay sampling
- [redacted]
- BCVA
- Microperimetry
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review
- Corticosteroid compliance review for treated subjects

10.6 Visit 6 (Month 4 ± 7 Days)

At Visit 6 (Month 4 ± 7 days), the following assessments will be performed (assessments can be spread over 2 consecutive days if necessary):

- Immunoassay sampling
- [redacted]
- BCVA
- Contrast sensitivity test
- Colour vision test
- Microperimetry
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF

- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

10.7 Visit 7 (Month 8 ± 14 Days)

At Visit 7 (Month 8 ± 14 days), the following assessments will be performed (assessments can be spread over 2 consecutive days if necessary):

- Immunoassay sampling
- [redacted]
- BCVA
- Contrast sensitivity test
- Colour vision test
- Microperimetry
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

10.8 Visit 8 (Month 12 ± 14 Days, End of Study Visit)

At Visit 8 (Month 12 ± 14 days), the following assessments will be performed (assessments can be spread over 2 consecutive days if necessary):

- VFQ-25[1]
- Vital signs
- Immunoassay sampling
- [redacted]
- BCVA
- Contrast sensitivity test
- Colour vision test
- Reading speed test[2]
- Microperimetry
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- 7-field colour fundus photography (including stereo photographs for fields 1, 2, and 3)

- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

1. VFQ-25 must be completed by subjects at the beginning of the study visit, prior to any significant interaction with study staff; the questionnaire is used only in languages in which it is validated.

2. The IReST speed reading test is only conducted in languages of which a validated translation is available.

10.9 Early Termination Visit

In the event that a subject discontinues the study at any time, the site should use every reasonable effort to ensure that an ET Visit is conducted. The following assessments should be performed:

- VFQ-25[1]
- Vital signs
- Immunoassay sampling
- [redacted]
- BCVA
- Contrast sensitivity test
- Colour vision test
- Reading speed test (if applicable)[2]
- Microperimetry
- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- 7-field colour fundus photography (including stereo photographs for fields 1, 2, and 3)
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

1. VFQ-25 must be completed by subjects at the beginning of the study visit, prior to any significant interaction with study staff; the questionnaire is also used only languages in which it is validated.

2. The IReST speed reading test is only conducted in languages in which a validated translation is available.

10.10 Unscheduled Visits

If clinically indicated, subjects may need to return to the site for an unscheduled visit. At a minimum, the following assessments will be performed.

- BCVA

- Full ophthalmic examination, including IOP, a slit-lamp examination, lens opacity, and dilated fundus examination
- SD-OCT
- AF
- AE/SAE monitoring
- Concomitant medication, procedures, and treatment review

11 ASSESSMENT OF EFFICACY

For all visits, an attempt should be made to perform all procedures in both eyes, as described in Table 3. If the subject is unable to complete a procedure due to poor vision in either eye, this should be clearly documented in the source documentation and that procedure can be missed for that eye. In the case that an assessment is missed, the reason should be clearly documented in the source notes.

11.1 VFQ-25 Questionnaire

Subjects will complete the VFQ-25 at the times indicated in Table 3. The VFQ-25 must be completed by the subject at the beginning of the study visit, before any significant interaction with the study staff.

This questionnaire measures dimensions of self-reported vision-targeted health status that are most important to persons with eye disease (Mangione 2001). Improvement in the VFQ-25 will be evaluated using individual scores, subscale scores, and the overall composite score. The VFQ-25 will only be conducted in languages in which a validated translation is available.

[redacted]

11.3 Best Corrected Visual Acuity

To evaluate changes in VA over the study period, BCVA will be assessed for both eyes using the ETDRS VA chart at the times indicated in Table 3.

The BCVA test should be performed prior to pupil dilation, and distance refraction should be carried out before BCVA is measured. Initially, letters are read at a distance of 4 metres from the chart. If <20 letters are read at 4 metres, testing at 1 metre should be performed. BCVA is to be reported as number of letters read correctly by the subject. At the Screening/Baseline Visit, eyes with a BCVA of 34-73 ETDRS letters (equivalent to worse than or equal to 6/12 or 20/40 Snellen acuity, but better than or equal to 6/60 or 20/200 Snellen acuity) will be eligible for the study.

If a subject cannot read any letters on the BCVA chart, the subject will be tested for finger counting, hand movements or light perception. Refer to the Site Operations manual for full details.

11.4 Contrast Sensitivity

Contrast sensitivity will be measured for both eyes at the times indicated in Table 3.

Contrast sensitivity will be measured prior to pupil dilation using a Pelli-Robson chart.

11.5 Colour Vision

Colour vision will be tested for both eyes prior to pupil dilation at the times indicated in Table 3.

Eyes will be tested separately and in the same order at each assessment. Refer to the Study Operations Manual for details on the colour vision test to be used.

11.6 Reading Speed Test

Reading performance will be evaluated prior to pupil dilation at the times indicated in Table 3 using International Reading Speed Texts (IReST), which provide standardised assessment of reading performance in 17 languages (Trauzettel-Klosinski 2012). The IReST will be provided to each site by the Sponsor, and for complete user instructions refer to the Study Operations Manual (which will include the randomisation procedure for text selection). The IReST will only be conducted in languages in which a validated translation is available.

11.7 Microperimetry

Microperimetry will be conducted for both eyes at the times indicated in Table 3.

Microperimetry will be conducted by certified technicians to assess changes in retinal sensitivity within the macula. All microperimetry images will be sent by the sites to a Central Reading Centre (CRC) for review. For complete technical specifications for microperimetry, refer to the Study Operations Manual (which will include procedures from the CRC regarding how measurements are to be taken).

11.8 Fundus Autofluorescence

To assess changes in the area of viable retinal tissue, fundus AF will be performed for both eyes at the times indicated in Table 3.

All fundus AF images will be performed by certified technicians at the site after dilation of the subject's pupil and sent to a CRC for review. For complete technical specifications for fundus AF, refer to the Study Operations Manual (which will include procedures from the CRC regarding how measurements are to be taken).

11.9 Spectral Domain Optical Coherence Tomography (SD-OCT)

SD-OCT will be performed for both eyes at the times indicated in Table 3.

SD-OCT measurements will be taken by certified technicians at the site after dilation of the subject's pupil. All OCT scans will be submitted by the sites to a CRC where the scans will be evaluated. SD-OCT will be used to assess a number of variables, including quantifying the integrity of the ellipsoid zone and reduction in the signal from the outer nuclear layer and choroid. In addition, since progressive foveal thickening has been noted in the early phase of CHM (Jacobson 2006), foveal changes will be assessed. For complete technical specifications for SD-OCT, refer to the Study Operations Manual (which will include procedures from the CRC regarding how measurements are to be taken).

12 ASSESSMENT OF SAFETY

12.1 Full Ophthalmic Examination

A full ophthalmic examination will be conducted for both eyes at the times indicated in Table 3.

For subjects in the AAV2-REP1 groups, the full ophthalmic examination will be conducted prior to pupil dilation and prior to vitrectomy and administration of study medication at the applicable study visit.

The ophthalmic examination will include IOP, slit lamp examination, lens opacity grading, and dilated ophthalmoscopy. The same slit lamp machine and lighting conditions should be used across study visits for any given subject.

In addition to the parameters listed above, relevant subjects will be carefully examined for the presence of intraocular inflammation after vector administration. Cataract can also develop as a result of the vitrectomy procedure and can potentially affect VA. Pre-operative grading of lens opacity and colour should therefore be documented by the established clinical lens opacities classification system. A recent study has shown that cataract surgery is effective in subjects with CHM and without any specific risks (Edwards 2015). Hence, if clinically indicated, subjects who develop cataracts may undergo cataract surgery. If cataract surgery is performed, it should be carried out at least 4 weeks before the Month 12 Visit/EOS Visit.

12.2 7-Field Colour Fundus Photography

To aid in the objective clinical assessment of progressive retinal changes, 7-field colour fundus photography will be performed for both eyes at the times indicated in Table 3.

Fundus photography will be performed by certified technicians following pupil dilation. Stereo photos should be performed for fields 1, 2, and 3. All fundus photographs will be sent by the sites to the CRC for review. For complete technical specifications for fundus photography, refer to the Study Operations Manual (which will include procedures from the CRC regarding how measurements are to be taken).

12.3 Evaluation, Recording, and Reporting Adverse Events

12.3.1 Definitions

12.3.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject, which does not necessarily have a causal relationship with the study medication/surgical procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication / surgical procedure, whether or not related to the investigational product or with the surgical procedure described in this protocol.

AEs are to also include any pre-existing condition (other than CHM) or illness which worsens during the study (i.e., increases in frequency or intensity).

12.3.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Results in vision loss or is vision threatening
- Is an other important medical event(s).

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.

Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute an SAE.

Other events that may not result in death, are not life threatening or do not require hospitalisation, may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Vision Loss to Be Reported as a Serious Adverse Event

Vision Loss NOT TO BE Reported as an SAE:

- Surgery-related BCVA decrease of ≥15 letters on ETDRS chart occurring within 1 day of surgery, but recovering / resolving at post-operative Days 7 and 14.

Vision Loss or Vision-Threatening Event TO BE Reported as an SAE:

- Surgery-related BCVA decrease of ≥15 letters on ETDRS chart that occurs within 1 day of surgery and that has not recovered* by the 1-Month Visit.
- A decrease in BCVA of ≥15 letters on ETDRS chart that occurs within 1 day of surgery, however, in the investigator's opinion:
    - Has an evolution not consistent with the expected post-operative course;
    - May be attributable to a complication that occurred during surgery, or another untoward event, or the study drug;
    - Actually or potentially requires any surgical or medical intervention to prevent permanent loss of vision.
- Non-surgery-related, sustained (>48 hours duration) decrease from baseline in BCVA of ≥15 letters on ETDRS chart.

***Recovery / Resolution of BCVA loss is defined as a return to baseline BCVA within 5 letters on the ETDRS chart.**

12.3.2 Recording of Adverse Events

AEs/SAEs will be collected from the time the subject provides written informed consent through the EOS Visit (or ET Visit or Unscheduled Visits, if applicable).

Subjects will be questioned on the occurrence of an AE at every visit including any unscheduled visit, by using non-leading questioning such as 'How have you been since the last visit?' This will include the telephone contact at Visits 2, 3 and 4 for subjects in the Control group.

All AEs occurring during the study observed by the investigator or reported by the subject, whether or not attributed to study medication or the surgical procedure, will be recorded in the subject's medical records and in the eCRF.

The following information will be recorded in the eCRF for each AE: description, date of onset and end date, outcome, severity, assessment of relatedness to study medication/study procedure, the action taken and confirmation of whether the event is considered serious (see Section 12.3.1.2 for the definition of seriousness). Follow-up information should be provided as necessary (see Section 12.3.3 for specifics on follow-up procedures).

AE severity and relationship to the study medication or the surgical procedure will be assessed at the site by the investigator or a medically qualified designee.

AE Severity

The severity of events will be assessed on the following scale:

1 = mild (awareness of sign or symptom, but easily tolerated)

2 = moderate (discomfort sufficient to cause interference with normal activities)

3 = severe (incapacitating, with inability to perform normal activities).

AE Relationship

When assigning relatedness of the AE, consideration will be given to whether there is a plausible relationship to either the study medication or the surgical procedure. The following are definitions of relatedness that will be used in this study.

Unrelated:	It is not reasonably related in time to the administration of the study medication/surgical procedure or exposure of the study medication/surgical procedure has not occurred
Related:	A reasonable possibility exists that the study medication / study procedure caused the AE. A suspected AE can be further defined by: *Possibly related:* clinically or biologically reasonable relative to the administration of the study medication/surgical procedure, but the event could have been due to another equally likely cause *Probably related:* is clinically/biologically reasonable relative to the administration of the study medication/surgical procedure, and the event is more likely explained by exposure to/administration of the study medication/surgical procedure than by other factors and causes

Definitely related: a causal relationship of the onset of the event, relative to administration of the study medication/surgical procedure exists and there is no other cause to explain the event.

When a relationship is determined to exist, the investigator or medical designee will further define if that relationship is to the *study medication*, the *study procedure*, *both*, or *unknown*.

12.3.3 Follow-up of Adverse Events

AEs will be followed until the subject has recovered or the subject's participation in the study is complete.

Subjects who are withdrawn from the study as a result of a drug-related AE will be followed up until the event has resolved, subsided, stabilised, or the subject withdraws consent or is lost to follow-up.

All SAEs, regardless of attribution to study medication or the surgical procedure, should be followed-up until the event has resolved, subsided, stabilised, or the subject withdraws consent or is lost to follow-up. The Sponsor (or designee) will follow up SAE reports to completion. Investigators are expected to provide the requested additional information for a complete assessment and documentation of the SAE reports within a timely manner.

12.3.4 Reporting of Serious Adverse Events

The investigator shall immediately (within 24 hours of learning of the event) report any SAE to the Sponsor (or its designee) by completing and emailing an SAE form. The initial report shall be promptly followed up with a more detailed report providing specifics about the subject and the event. Copies of hospital reports, autopsy reports, and other documents should be provided (if applicable).

The sponsor may unmask any SAE reports that are serious, unexpected, and related to the study drug, as required, in accordance with safety reporting guidance and regulations.

The Sponsor will report SAEs and Suspected, Unexpected, Serious Adverse Reactions (SUSARs) to investigative sites, IRBs/IECs and regulatory authorities in compliance with current legislation. All cases that are fatal or life-threatening will be reported immediately after the Sponsor received the initial report from the Investigator. All non-fatal or non-life-threatening cases will be reported within a maximum of fifteen days after the initial Investigators report. The Sponsor will also provide periodic safety reports to IRBs/IECs and regulatory authorities as applicable. Follow-up SAE reports will be submitted within 15 days of receiving the information.

A sample SAE form is provided in the Study Operations Manual, along with the SAE reporting contact information.

12.3.5 Procedures for Unmasking

The Investigator has the ability to unmask an individual subject's treatment assignment in order to provide emergency treatment. Unmasking is appropriate when knowledge of the subject's dose would affect the medical management of the subject.

If the Investigator determines unmasking is required, then s/he unmasks the subject through the Electronic Data Capture (EDC) system, files the resulting confirmation in a restricted file

until the end of the study, and notifies the Medical Monitor within 24 hours that the subject's treatment assignment has been unmasked. The Investigator will not communicate the treatment assignment to the Medical Monitor or to any sponsor or study team staff; nor should the treatment assignment be communicated to site staff other than those personnel who require that knowledge in order to treat the subject.

The Investigator will ensure that the rationale, date, and time of unmasking is noted in the subject's source documentation, but not the treatment assignment. The medical emergency that necessitated unmasking must also be recorded in the source documentation and the case report form per standard study procedures.

12.3.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be used in this study to safeguard the safety and interests of study subjects and assess the safety and risk/benefit of the gene therapy intervention during the trial.

At regular intervals during the study, the DMC will review the progress and accrued study data. The DMC will inform the Sponsor if there is a consensus that the ongoing data show that the gene therapy, its method of administration, and/or the study design are no longer in the best interests of study subjects. Details of DMC organisation and responsibilities are included within a DMC charter that has been approved by all committee members.

12.4 Pregnancy

Any pregnancy that occurs during the clinical study in a female partner of a study subject should be recorded on a Pregnancy Notification Form. Subject consent is required prior to the collection of personal data, however, the investigator shall immediately (within 24 hours of learning of the event) report the pregnancy, with at least preliminary data, to the Sponsor (or its designee) by completing and emailing the Pregnancy Notification Form. In addition, if possible, outcome of the pregnancy fathered by the subject should be recorded, including any congenital abnormality or birth defect.

12.5 Laboratory Assessments

12.5.1 Immunogenicity

For the evaluation of immunogenicity, blood will be collected at the times indicated in Table 3. Select samples may be analysed.

Immunoassays are planned to assess antibody and cell-based responses against AAV2-REP1. Immunoassays may or may not be conducted on these samples, depending on safety findings from Investigator Sponsored studies and ongoing NightstaRx sponsored studies with AAV2-REP1. If immunoassays are conducted, ELISPOT assays will be used for T-cell mediated immune responses to transgene, and antibody responses will be assayed using ELISA- and cell-based methods.

All immunogenicity samples will be sent to a central laboratory for analysis. Refer to the Study Operations Manual for details on the shipping and handling of samples.

Remaining samples may be stored for up to 15 years or per local regulations.

12.6 Vital Signs

Vital signs (pulse and systolic and diastolic blood pressure) will be taken at the times indicated in Table 3.

Vital signs should be taken after the subject is seated for at least 5 minutes.

13 STATISTICAL CONSIDERATIONS

Details of the statistical analyses will be described separately in the STAR Statistical Analysis Plan.

13.1 Sample Size

Approximately 160 subjects will be enrolled in the study (64, high dose group; 32, low dose group; 64, control group).

The sample size calculation is based on a Fischer's exact test. CHM is a degenerative disease, it is therefore assumed that a ≥15 letter BCVA gain would not be observed in subjects without CHM treatment. Assuming that 16.7% of the treated subjects will gain ≥15 letters BCVA at Month 12, 56 subjects in the high dose group and the control group provide at least 90% power at a 0.05 level of significance with a 2-sided test. To be conservative, 64 patients in the high dose group and 64 patients in the control group is needed to ensure 85% power in case 1 patient in the untreated control group has ≥15 letter BCVA gain by chance, which corresponds to a total of 160 patients completing the study.

13.2 Procedure for Accounting for Missing Data

All reasonable efforts will be made to obtain complete data for both eyes on all subjects. However, missing observations may occur. Management of dropout and missing observations will depend on their nature and frequency.

For binary efficacy endpoints (including the primary efficacy endpoint), missing data will be imputed as failure, to be conservative. For the continuous efficacy endpoints, the last observation carried forward (LOCF) approach will be utilized for handling missing data.

To evaluate the robustness of the results of the main analyses, sensitivity analyses of the primary and secondary endpoints will be performed. These analyses will include different imputation methods on different analysis sets and will be described in detail in the Statistical Analysis Plan.

Safety data will be analysed on observed data. Missing data will not be imputed.

13.3 Analysis Population

13.3.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population is defined as all subjects who are randomised, receive the study treatment (or the phone call for those in the untreated control group), and have at one least one post-treatment BCVA measurement.

The ITT population will be used for the efficacy, quality of life, and [redacted].

The primary population for efficacy analysis is the ITT population. Subjects will be analyzed based on the treatment to which they were randomised.

13.3.2 Per Protocol Population

The Per Protocol (PP) population is a subset of the ITT Population, whereby subjects with major protocol deviations that may affect substantially the results of the efficacy endpoints, are excluded. Subjects will be analysed according to their actual treatment received.

The determination of the major protocol deviations, and therefore the composition of the Per Protocol Set, will be made prior to unmasking and will be documented separately.

The PP population will be used to analyze the primary and key secondary efficacy endpoints.

13.3.3 Safety Population

The Safety population includes all subjects randomised and who attended Visit 2 (either received study treatment [AAV2-REP1] or a study visit Telephone Call [Control]).

Subjects will be analysed according to their actual treatment received.

The Safety population will be used for all safety analyses.

13.4 Descriptive Statistics

Continuous variables (including changes from Baseline) will be summarised over time using descriptive statistics (i.e., mean, standard deviation, 95% confidence interval [CI], median, first and third quartiles, fifth and ninety-fifth percentiles, minimum, and maximum). Categorical variables (including shifts from Baseline) will be described over time using counts, percentages, and 95% CIs.

13.5 Demographics and Baseline Characteristics

In order to establish whether treatment groups are comparable, demographics will be summarised by treatment group and overall subjects. Baseline ocular characteristics will be summarised by eye and treatment group.

In the event Baseline data from Visit 1 (prior to treatment) are missing or unavailable, then available data from Visit 2 (prior to treatment) will be used as the Baseline value.

13.6 Efficacy Analyses

Statistical tests will be performed at the alpha level of 0.05 (unless otherwise specified). Statistical tests and 95% CIs will be 2-sided.

13.6.1 Primary Efficacy Endpoint

The primary endpoint will be calculated as the proportion of subjects with a ≥15-letter increase from baseline in BCVA at the Month 12 visit.

The primary endpoint will be summarised using the summary statistics for categorical data including the 95% CI.

The primary endpoint will be compared between study arms (high dose vs control, low dose vs control) using the Fisher's Exact test. The primary approach will be the unstratified analysis, and a supportive analysis will be conducted with the Cochran-Mantel-Haenszel approach by stratifying by Surgery Group. As Fisher's Exact test is overly conservative when the number of events is low, a supportive analysis will be conducted using Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001 (Berger 1994). To maintain the

test at 0.05 two-sided level, the reported p-value will be 2 times the one-sided p-value from the Fisher's Exact-Boschloo test.

The primary analysis of the primary endpoint will be based on the ITT population, and a supportive analysis will be performed based on the PP population.

13.6.2 Key Secondary Efficacy Endpoints

There are three key secondary endpoints as summarised in Table 2.

The continuous efficacy endpoint will be analyzed by the analysis of covariance (ANCOVA) model including Surgery Group, baseline value of the assessment, and study arms. Missing data will be handled by the LOCF approach.

The binary efficacy endpoints will be analyzed similar to the primary efficacy endpoint.

The least square (LS) means, standard error (SE) and 95% CI will be reported for each treatment at each post randomisation visit. Least square mean, SE, 95% CI, and p-value for the between group differences will also be provided.

The primary analysis of the key secondary endpoints will be based on the ITT population, and a supportive analysis will be performed based on the PP population.

Table 2 Statistical Tests for Key Secondary Efficacy Endpoints

	Key Secondary Endpoint	Statistical Method
1	Change from Baseline in BCVA at Month 12 measured by the ETDRS chart	ANCOVA
2	Proportion of subjects with a ≥10-letter improvement from Baseline in BCVA at Month 12 measured by the ETDRS chart	Fisher's Exact Test; Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001; CMH Approach
3	Proportion of subjects with no decrease from Baseline in BCVA or a decrease from Baseline in BCVA of <5 ETDRS letters at Month 12 measured by the ETDRS chart	Fisher's Exact Test; Fisher's Exact-Boschloo test with a Berger-Boos correction of beta=0.001; CMH Approach

Abbreviations: BCVA= best corrected visual acuity, CHM= choroideremia, ETDRS=Early Treatment of Diabetic Retinopathy Study

13.6.3 Other Secondary Efficacy Endpoints

Categorical secondary endpoints will be summarised and analysed using the same procedure as the categorical primary endpoint.

The continuous secondary endpoints will be summarised using the summary statistics for continuous data, including the 95% CI. The treatment difference in change from baseline and its 95% CI will be calculated based on the LSMEANS of the ANCOVA model including Surgery Group, baseline value of the assessment, and study arms. Change from baseline will be compared between study arms (high dose vs control, low dose vs control) using the above ANCOVA model. For the Overall Composite Score of VFQ-25, the covariates Age and Race will be added to the model.

13.6.4 Multiplicity Control

The protection of the type I error for the comparison between the high dose and the untreated control under a hierarchical procedure. The primary efficacy endpoint will be first tested. If the p-value is <0.05, the study will be declared positive and the key secondary endpoints will

be tested in the pre-specified order. The comparison between the low dose arm and the untreated control is considered as supportive, and will be performed only if significance is achieved between the high dose and the untreated control.

No adjustment will be performed for DMC reviews.

13.7 Safety Analyses

No significance testing will be performed for safety analyses. Safety analyses will be descriptive, with 95% CIs calculated where appropriate.

13.7.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Affairs version 21 or higher. Events will be summarised by system organ class, preferred term, and group. Both the number of eyes/subjects experiencing an AE and the number of events will be summarised. Similar summaries will be produced for study drug/procedure-related AEs, AEs leading to discontinuation, and SAEs. AEs will also be summarised by maximum severity, relationship to study drug/procedure, and time to onset and resolution.

13.7.2 Full Ophthalmic Examination

Intraocular pressure and change from Baseline in IOP will be summarised by visit, by treatment and by eye. Abnormal slit lamp examination findings and dilated ophthalmoscopy findings, and shift from Baseline will be summarised by visit, by treatment and by eye.

Lens opacity categories and shift from Baseline will be summarised by visit, by treatment and by eye.

13.7.3 7-Field Colour Fundus Photography

Categories of colour fundus photography findings and shift from Baseline will also be summarised by visit, by treatment and by eye.

13.7.4 Laboratory Assessments and Vital Signs

Laboratory assessments (immunogenicity) and vital signs will be summarised in a descriptive manner.

14 INFORMED CONSENT, ETHICAL REVIEW AND REGULATORY CONSIDERATIONS

14.1 Informed Consent

Subjects with CHM who meet all of the entry criteria will be invited to take part in the study. Subjects must personally sign and date the latest IEC/IRB approved version of the informed consent form before any study-specific procedures are performed.

Written and verbal versions of the subject information and informed consent will be presented to the subjects detailing no less than: the exact nature of the study; the implications and constraints of the protocol; expectations of their participation and the known side effects and any risks involved in taking part. It will be clearly stated that the subject is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The subject will be allowed as much time as needed to consider the information and the opportunity to question the investigator, their primary care physician/general practitioner or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of subject dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the investigator. A copy of the signed informed consent will be given to each subject. The original signed form will be retained at the study site and an additional copy will remain in the subject's medical records.

This is a single-masked study. Therefore, all subjects will be informed at the time of randomisation whether they have been randomised to the AAV2-REP1 or Control group. However, subjects in the AAV2-REP1 treatment groups will be masked to the assigned dose.

For subjects in the AAV2-REP1 treatment groups having surgery at a different site, it may be necessary to sign a separate surgical consent form at that location.

The informed consent must be signed within 12 weeks prior to the treatment visit (Visit 2, Day 0).

14.2 Ethical/Regulatory Review

The protocol, informed consent form, subject information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (IEC or IRB), regulatory authorities, and host institution(s) for approval. If there are any changes to the approved protocol (with the exception of emergency modifications required for the subject's safety), a protocol amendment will be issued by the Sponsor. When required by local law, the IEC/IRB and Competent Authority must give approval of any amendments likely to affect the safety of subjects or study conduct. Each site must maintain accurate and updated records of all correspondence with the IEC/IRB.

14.3 Regulatory Considerations

The study will be conducted in full conformity with all applicable laws and regulations, including the International Council on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) (CPMP/ICH/135/95).

As permitted, the study will be conducted in accordance with the relevant articles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in 1964 and as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000), Washington (2002), Tokyo (2004), Seoul (2008), and Brazil (2013).

15 ADMINISTRATIVE PROCEDURES

15.1 Data Quality Control and Assurance

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

The Sponsor and its selected vendors have systems in place for implementing and maintaining quality assurance and quality control systems, with written Standard Operating Procedures to ensure that all aspects of the trial will be conducted in compliance with this protocol and data will be generated, documented and reported in compliance with this protocol.

Data will be entered into a validated clinical study database and subject to programmed validation checks and manually verified for accuracy and completeness by a Sponsor's representative, both remotely and during on-site monitoring visits. Any discrepancies will be resolved with the investigator or designee, as appropriate.

Regular monitoring will be performed by the Sponsor or its designee according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

In addition, this study will be subject to quality assurance audits in order to independently verify compliance with the protocol.

15.2 Data Handling and Records Management

The investigator must maintain adequate and accurate source documents, which will be the basis of information for the eCRFs. The source documents are to be separate and distinct from the eCRFs. All study data will be entered on an encrypted electronic data capture system with pass-codes known to all investigators and appropriately delegated study team members only. This electronic data entry system has been validated. Incomplete or inconsistent data will result in data queries that require resolution by the investigator or designee.

The investigator must ensure that clinical study records are retained according to national regulations. The investigator must immediately inform the Sponsor if any documents are to be destroyed, transferred to another facility, or transferred to a different owner.

In addition, files containing photos or digital outputs will be electronically transmitted to the reading centre for centralised, standardised review.

Samples will also be provided to a central laboratory for potential analysis of immunogenicity. Results from these analyses, if conducted, will also be provided as an external data set that will be loaded directly into the study database.

The investigator must retain sufficient documentation that these images, outputs, and samples were handled and transmitted appropriately.

15.3 Access to Source Documentation and Subject Privacy

Direct access will be granted to authorised representatives from the Sponsor (or designee), host institution, the IEC/IRB, and regulatory authorities to permit trial-related monitoring, audits and inspections.

The trial staff will ensure that the subject's anonymity is maintained. All documents will be stored securely and only accessible by trial staff and authorised personnel. Subjects will be identified by a subject ID number on the eCRF and any electronic database. The subject's name and any other identifying detail will NOT be included in any study data electronic file. The study will comply with the data protection laws which require data to be anonymised as soon as it is practical to do so.

Subject medical information obtained in this study is confidential, and disclosure to third parties other than those noted below is prohibited. As required by Personal Information Protection and Electronics Documents Act and Personal Health Information Protection Act, upon the subject's written permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Data generated by this study must be available for inspection by regulatory agencies, national and local health authorities, the Sponsor or their representative, and the IRB.

15.4 Time and Schedule of the Study

The study includes 12 months of follow-up post-treatment, and 8 weeks for screening, for a total of approximately 14 months per subject.

15.5 Policy for Publication and Presentation of Data

The detailed procedures for publications and data presentations are set out in the clinical trial agreement entered into with the Sponsor (or designee) in connection with this study.

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17 APPENDICES

17.1 Schedule of Study Procedures

Table 3 presents a schedule of study procedures.

Table 3 Schedule of Study Procedures

Visit	Visit 1[a]	Visit 2[b]	Visit 3[b]	Visit 4[b]	Visit 5[a]	Visit 6[a]	Visit 7[a]	Visit 8[a, c]	Early Termination[d]	Unscheduled Visit[e]
Study Day/Visit Window	**Screening/ Baseline[f]**	**Day 0 *Injection Day***	**Day 1 *Post op***	**Day 7 *Post op* ± 3d**	**Month 1 ± 7d**	**Month 4 ± 7d**	**Month 8 ± 14d**	**Month 12 ± 14d**		
Informed Consent	X									
Demographics, medical and ocular history	X									
Immunoassay blood sampling (ELISA and cell-based methods)[g]	X		X	X	X	X	X	X	X	
Immunoassay blood sampling (ELISPOT)[g]	X			X	X	X	X	X	X	
VFQ-25[h]	X							X	X	
Vital Signs	X		X	X	X			X	X	
Weight[i]	X									
BCVA[k]	X		X	X	X	X	X	X	X	X
Full ophthalmic exam[l]	X	X	X	X	X	X	X	X	X	X
SD-OCT	X		X	X	X	X	X	X	X	X
Autofluorescence	X			X	X	X	X	X	X	X
Microperimetry	X				X	X	X	X	X	
Contrast sensitivity[m]	X					X	X	X	X	
Colour vision	X					X	X	X	X	
7-field colour fundus photos[n]	X							X	X	
Reading speed test[o]	X							X	X	
Randomisation	X									
Corticosteroid dispensation/accountability[p]	X	X	X	X	X					
Study drug/sub-retinal injection/vitrectomy/ retinal detachment		X[r]								
AE/SAE monitoring[q]	X	X	X	X	X	X	X	X	X	X

Visit	**Visit 1**[a]	**Visit 2**[b]	**Visit 3**[b]	**Visit 4**[b]	**Visit 5**[a]	**Visit 6**[a]	**Visit 7**[a]	**Visit 8**[a, c]	**Early Termination**[d]	**Unscheduled Visit**[e]
Study Day/Visit Window	**Screening/ Baseline**[f]	**Day 0** ***Injection Day***	**Day 1** ***Post op***	**Day 7** ***Post op*** **± 3d**	**Month 1 ± 7d**	**Month 4 ± 7d**	**Month 8 ± 14d**	**Month 12 ± 14d**		
Concomitant medication, procedures and treatment review	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; BCVA=best corrected visual acuity; ELISA=enzyme-linked immunosorbent assay: ELISPOT=enzyme-linked immunospot; ET=early termination; IOP=intraocular pressure; [redacted]; SAE=serious adverse event; SD-OCT=spectral domain optical coherence tomography; VFQ-25=25-item Visual Function Questionnaire.

NOTE: An attempt should be made to perform all procedures in both eyes, unless otherwise specified. Each eye should be tested separately. If the subject is unable to complete a procedure due to poor vision in either eye, this should be documented in the source notes and the assessment not completed for that eye.

Assessments with gray shading are to be assessor-masked.

[a] Visit may be performed over 2 consecutive days if necessary.

[b] Study Visits 2, 3, and 4 only apply to subjects in the AAV2-REP1 groups. For subjects in the Control group, a telephone contact will be made at Visits 2, 3, and 4, and information regarding AEs/SAEs and concomitant medications, procedures, and treatments will be recorded.

[c] End of Study Visit.

[d] An ET visit should be performed if a subject discontinues at any time.

[e] If clinically indicated, subjects may need to return to the site for an unscheduled visit. At a minimum, all assessments listed will be performed.

[f] Informed consent must be signed within 12 weeks prior of dosing (Visit 2). The Screening/Baseline Visit must be performed within 8 weeks of dosing (Visit 2). Assessments and procedures conducted in the final visit of the NIGHT study (including the ET Visit) may be used for the Screening/Baseline Visit if the final NIGHT study occurs within 8 weeks prior to dosing (Visit 2).

[g] Samples will be taken and retained for analyses, if necessary.

[h] VFQ-25: to be completed only at sites where a validated translation is available. VFQ-25 must be completed by subjects at the beginning of the study visit, before any significant interaction with the study staff.

[i] Weight is assessed for dose calculation for 21-day corticosteroid regimen.

[redacted]

[k] In order to capture accurate BCVA values at Visit 1 (Screening/Baseline), the following conditions apply to the BCVA assessment:

If the BCVA value at Visit 1 (Screening/Baseline) is ≥ ±10 letter gain or loss in the study eye compared to the previous NIGHT study visit (if applicable), then BCVA must be repeated an additional 2 times, resulting in a total of 3 BCVA measures at Visit 1. To facilitate the additional BCVA measures this visit should be conducted over 2 days, with BCVA measured twice on Day 1 and once on Day 2. All 3 BCVA values must be recorded in the eCRF. The highest score will be used to define subject eligibility.

If the BCVA value at Visit 1 (Screening/Baseline) is < ± 10-letter difference in the study eye compared to the previous NIGHT study visit (if applicable), then BCVA will be collected once and will not be repeated.

If the subject was not previously in the NIGHT study, BCVA assessments at baseline must be performed in triplicate over a period of 2 days, as described above. At least 2 of the triplicate values must meet BCVA eligibility requirements for inclusion in the study and the difference between the 3 assessments may not be ≥ 10 letters.

[l] The full ophthalmic examination will include assessments of IOP and lens opacity, a slit lamp examination, and dilated ophthalmoscopy. The same slit lamp machine and lighting conditions should be used across the study for each subject.

[m] Pelli Robson chart will be used for contrast sensitivity.

[n] Stereo photos for Fields 1, 2, 3.

[o] International Reading Speed Texts. To be completed only in languages for which a validated translation is available.

[p] For AAV2-REP1-treated subjects, only: corticosteroid (prednisone/prednisolone) will be dispensed at Visit 1 or at least 2 days prior to Visit 2 with instruction to start treatment 2 days before the planned surgical date, and to continue for 21 days in total.

[q] AEs/SAEs will be collected from the time the subject provides written informed consent through the End of Study Visit (or ET Visit or Unscheduled Visits, if applicable).

[r] For subjects in the AAV2-REP1 groups only. On the Injection Day Visit (Visit 2, Day 0), all subjects in the AAV2-REP1 groups will undergo vitrectomy and treatment with AAV2-REP1.

Summary of STAR Protocol Changes: Version 1 to Version 4

Protocol Version	Primary Endpoint	Secondary Endpoint	Substantial Change and Rationale	Submitted to Regulatory Authority	Subjects Enrolled Under Version (Implemented)
Protocol version 1.0 17 Sept 2015	Proportion of subjects with a ≥10 letter improvement at Month 6	Proportion of subjects with a ≥15 letter improvement at Month 6	N/A	No; Internal document	None
Amendment 1, Version 2 10 Nov 2015	Same	Same	• Removed bilateral treatment in 4-6 subjects with 5 weeks of screening for study eye 1 as decision was made to add a separate bilateral treatment study to the program	No; Internal document	None
Amendment 2, Version 3. 26 Feb 2016	Same	Same	• Change volume of gene therapy to be dosed from 0.05 mL to 0.1 mL (this was the volume tested and found safe in the ISTs) • Changed BCVA from 34-78 to 34 -73 (3-lines of vision loss allowed for a modifiable window of improvement; allowing 78 letters BCVA may have introduced a ceiling effect in subjects with milder impairment of vision • Removed randomization method for selection of study eye to worst eye based on PI opinion to limit impact of any detrimental effects of the surgery or treatment.	• Submitted in IND opening [redacted] • Submitted to UK CTA submitted to Germany	None

Protocol Version	Primary Endpoint	Secondary Endpoint	Substantial Change and Rationale	Submitted to Regulatory Authority	Subjects Enrolled Under Version (Implemented)
			Randomization to either treated or control group still occurred post-selection of study eye		
Amendment 2.1, Version 3.1 14 Apr 2016 UK ONLY	Same	Same	• DMC added with more details provided • Clarified safety reporting to all sites and IRBs and RA • Removed notation of patient registry as only study-specific safety follow-up measures are included in the protocol. Details of a patient registry are to be added to a separate protocol (then changed to long-term study Solstice) • Clarified time of contraception exclusion	To MHRA CTA UK	None
Amendment 2.2, Version 3.2 Germany 8 Sept 2016	Same	Same	• Added exclusion criteria of intraocular surgery in study eye in previous 6 months as this could have been a confounding factor in the interpretation of the study data	To PEI, Germany Only	None

Protocol Version	Primary Endpoint	Secondary Endpoint	Substantial Change and Rationale	Submitted to Regulatory Authority	Subjects Enrolled Under Version (Implemented)
Amendment 3, version 4 1 Aug 2017	Proportion of subjects with a ≥15 letter gain at 12 months	Proportion of subjects with a ≥15 letter gain at 12 months when compared to change in BCVA over 12-month period in historical control (NIGHT) (paired comparison pre-treatment to post-treatment	• Low dose added to support masking per recommendations from regulatory bodies • Sample size increased from 100 to 140 due to addition of low dose • Primary endpoint changed from ≥10 to ≥15-letter improvement per recommendations from FDA; follow-up also lengthened to 12 months due to feedback from FDA • Key secondary endpoint added as NIGHT paired comparison to historical data to complement the comparison to the parallel untreated control group	• Submitted [redacted] IND • All subjects randomized in this version, the current protocol version	83 Randomized: 51 Treated 29 Controls 3 Discontinued prior to Visit 2 (as of 22 NOV 2018)