CLINICAL STUDY PROTOCOL

NCT02553135

AAV2-REP1

An open label Phase 2 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)

INDICATION:	Choroideremia
STUDY PHASE:	Phase II
PRINCIPAL INVESTIGATOR:	Byron L. Lam MD
SPONSOR:	Bascom Palmer Eye Institute University of Miami 900 NW 17 Street Miami, Florida, USA 33136
FINAL PROTOCOL DATE:	18 May 2015

SPONSOR APPROVAL PAGE

Protocol Title:	An open label Phase 2 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)
Protocol Date:	18 May 2015
Approved By:	

The person(s) listed below are authorized to sign the protocol on behalf of Bascom Palmer Eye Institute, University of Miami.

Signed: _____ Date: _____

Name: Byron L Lam

Title: Professor of Ophthalmology

PRINCIPAL INVESTIGATOR'S SIGNATURE PAGE

Protocol Title:	An open label Phase 2 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)
Protocol Date:	18 MAY 2015

I have read the Investigator's Brochure for AAV2-REP1 I have read Protocol CHM-01 and agree to conduct the study as outlined and in compliance with the Declaration of Helsinki, the International Conference on Harmonization guideline for Good Clinical Practice, 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: _____

Byron L. Lam, M.D.
Professor
Bascom Palmer Eye Institute
University of Miami School of Medicine
Miami, Florida

CONTACT INFORMATION

Information is considered confidential.

1 PROTOCOL SYNOPSIS

Name of Sponsor/Company: Investigator Sponsored Study	
Name of Test Product: AAV2.REP1	
Dose(s): 0.1ml containing 10^{11} AAV2 genome particles	
Title of Study: An open label Phase 2 clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector (AAV2) encoding Rab-escort protein 1 (REP1)	
Study centre(s): Single center Investigator Sponsored trial	
Study period: 24 months (additional follow up will occur as per local requirements, but will not be covered within the scope of this study/protocol)	**Phase of development:** Phase 2
Key Objective of Study: To assess the anatomical and functional outcomes, as well as the safety of a single subretinal injection of AAV2.REP1 in subjects with genetically confirmed choroideremia for up to 24 months.	
Primary Endpoint: Change from baseline in best corrected visual acuity in treated eye, compared to untreated control eye	
Secondary Endpoints: ■ Change from baseline in autofluorescence evaluation in treated eye, compared to untreated control eye ■ Change from baseline in central visual field using microperimetry readings in treated eye, compared to untreated control eye [redacted] ■ Safety evaluation during the study	
Methodology: Open label single center study	
Number of subjects (planned): 6 patients	
Key Inclusion Criteria: • Participant is willing and able to give informed consent for participation in the study. • Male aged 18 years or above. • Genetically confirmed diagnosis of choroideremia. Active disease visible clinically within the macula region Best-corrected visual acuity equal to or worse than 6/9 (20/32; Decimal 0.63; LogMAR 0.2) but better than or equal to 6/60 (20/200; Decimal 0.1; LogMAR 1.0) in the study eye. **Key Exclusion Criteria:** • Female and child participants (under the age of 18) • Participants with a history of amblyopia in the study eye • Men unwilling to use barrier contraception methods, if relevant • Grossly asymmetrical disease or other ocular morbidity which might confound use of the fellow eye as a long-term control	

[redacted] Any other significant ocular and non-ocular disease/disorder [redacted]

[redacted] Contraindication to use of medications or contrast agents [redacted]

- Participants who 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: 0.1ml of AAV2.REP1, containing 10^{11} genome particles, administered as a single subretinal injection

Reference therapy (Comparator), dosage and mode of administration:
Fellow eye as comparator. The fellow eye will not receive any study treatment.

Outcome Measures used to evaluate endpoints: per protocol

Statistical methods:

Some information is considered confidential.

Summary statistics will be presented for both eyes (Treated Eye versus Control Eye groups). No formal statistical comparison will be performed (no p-value will be computed). For categorical/binary data, the number and proportion of patients pertaining to each category will be presented with its 95% Confidence Interval (CI). For continuous data, mean (and its 95% CI) and Standard Deviation (SD) will be presented.

[redacted]

[redacted]

[redacted]

Adverse events will be listed.

[redacted]

2 TABLE OF CONTENTS

3 ABBREVIATIONS AND DEFINITIONS

Abbreviation or Term	Definition
AAV2	Adeno-associated viral vector (serotype 2)
AE	Adverse event
BCVA	Best corrected visual acuity
BSS	Balanced salt solution
CBA	Chicken Beta Actin promoter
CHM	Choroideremia
CI	Confidence interval
CRF	Case Report Form
CRP	C-reactive protein
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
ETDRS	Early treatment diabetic retinopathy study
ET	Early termination
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
LOCS	Lens Opacities Classification System
PCR	Polymerase chain reaction
PI	Principal Investigator
REP1	Rab escort protein 1
SAE	Serious Adverse Event
OCT	Optical Coherence Tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction

4 INTRODUCTION

4.1 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 et al., 1990; Seabra et al., 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 et al., 1992; MacDonald et al., 2009).

4.2 Gene Therapy with Adeno-Associated Viral (AAV) Vectors

Adeno-associated virus (AAV) is a parvovirus containing single stranded DNA. There are many different AAV subtypes, each with slightly different DNA sequences and capsid proteins. AAV serotype 2 (AAV2) is the vector proposed in this study. The wild-type AAV2 genome lacks many of the viral sequences necessary for packaging of viral particles and has evolved to become dependent on adenovirus for replication and spread from infected cells. For most of the time 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 wildtype AAV2 antibodies can be detected in about 30% of humans (Mingozzi et al, 2007). Over time, the wildtype AAV2 genome may become integrated into chromosome 19 (Dutheil et al., 2009).

The non-immunogenic features of AAV2 make it ideal for gene therapy. The principle being to remove the wildtype 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 total size of the AAV2 genome is 4,700 base pairs and this must include the inverted terminal repeat (ITR) sequences which remain at either end of the transgene (Lusby et al., 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 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 subretinal 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 subretinal injection in non-human primates (Jacobson et al., 2006; Stieger et al., 2006; Vandenberghe et al., 2011). These are the cells which are primarily affected by the absence of REP1 in choroideremia, which correlates with the natural targeting of AAV2 delivered by subretinal injection. Hence the AAV2 serotype is an ideal vector to treat this condition.

4.3 Rationale

Choroideremia is a disease that causes blindness, with no available treatment option. The initial results from 6 patients included in a Phase I/II study (MacLaren et al., 2014) show the investigational gene therapy medicinal product being well tolerated and although the study is not powered to show efficacy there are functional improvements in vision following retinal detachment and subfoveal injection of AAV2-REP1 (0.6-1.0 x 1010 genome particles),

performed under general anesthesia. The initial results of this investigational retinal gene therapy trial are consistent with improved rod and cone function that overcome any negative effects of retinal detachment. These findings lend support to further assessment of AAV2-REP1 gene therapy in the treatment of choroideremia.

5 STUDY OBJECTIVES

5.1 Key Objective

To assess the anatomical and functional outcomes, as well as the safety of a single subretinal injection of AAV2-REP1 in subjects with genetically confirmed choroideremia for up to 24 months.

5.1.1 Primary Endpoint

- Change from baseline in best corrected visual acuity in treated eye, compared to untreated control eye

5.1.2 Secondary Endpoints

- Change from baseline in autofluorescence evaluation in treated eye, compared to untreated control eye
- Change from baseline in central visual field using microperimetry readings in treated eye, compared to untreated control eye

[redacted]

- Safety evaluation during the study

6 INVESTIGATIONAL PLAN

Information is considered confidential.

6.1 Summary of Study Design

This is a Phase II, open label study involving a total of 6 male patients with a clinical phenotype of choroideremia and a confirmed CHM genotype. The study will be conducted at the Bascom Palmer Eye Institute, University of Miami. Following consent, patients will be required to attend an initial screening visit. [redacted] patients will undergo a surgical procedure under general anesthesia which will include a standard vitrectomy, retinal detachment and administration of a subretinal injection of AAV2-REP1 ($1x10^{11}$ genome particles). Patients will be required to attend [redacted] study visits [redacted] over a 24 month period for functional, and anatomical assessments as well as monitoring of adverse events.

[redacted]

[redacted]

6.2 Screening Visit

[redacted]

6.3 Surgery

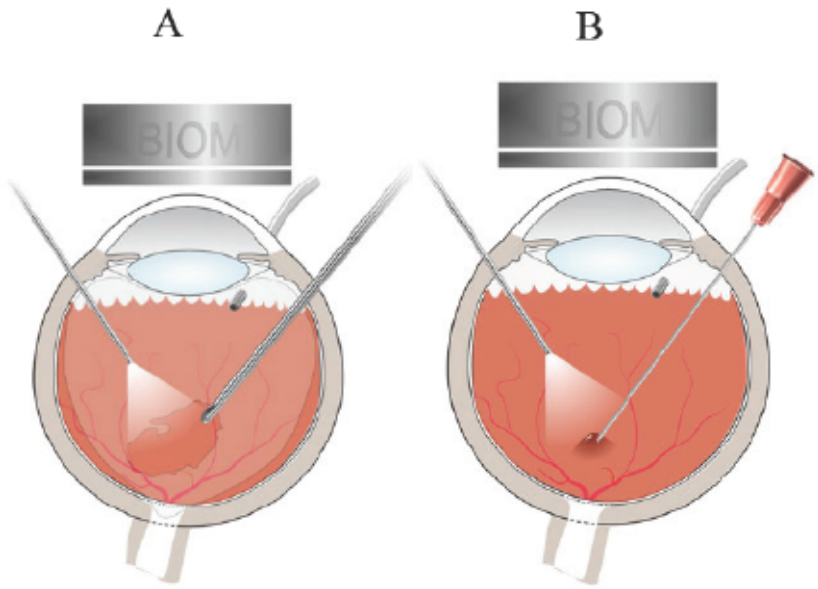
[redacted] Patients will be questioned for the occurrence of adverse events. A standard ophthalmic examination will occur prior to surgery to exclude any changes that might have occurred since the screening visit (see Table 1).

[redacted]

All surgery will take place in the Anne Bates Leach Eye Hospital using the standard vitrectomy system. A 23 gauge sutured approach would be used to avoid any potential risks of wound leakage. Patients would undergo a standard vitrectomy and detachment of the posterior hyaloid (Figure 1).

The vector needs to be primed in the 1 ml syringe in order to avoid formation of air bubbles. Injection can be manually performed or by connection to the viscous fluid injector function of the vitrectomy machine. The subretinal 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 subretinal fluid overlies all edge boundaries of the central region that has yet to undergo chorioretinal degeneration, as identified by fundus autofluorescence. Targeting of AAV2-REP1 to the most dynamic leading edge of the degeneration will maximize the chance of identifying a treatment effect within the two year study timeframe. Care will be taken during and after the surgery to limit potential vector spread by appropirate barrier protection for staff and appropriate disposal of drapes, instruments and fluids used during the surgery.

Figure 1 **Subretinal injection of AAV2 vector**



(A) A standard vitrectomy through the BIOM operating system to remove the vitreous gel, is followed by (B) injection of 0.1 ml vector suspension through a 41 g cannula into the subretinal space.

Patients will be carefully monitored for the occurrence of Adverse Events peri- and post-operatively. All adverse events, irrespective of relationship to the study drug and/or the surgical procedure will be captured in the patient's medical record and reported in the Case Report Forms (CRF) (see Section 9.2.8).

6.4 Follow up Visits

Information is considered confidential.

[redacted]

Adverse events, irrespective of relationship to the study drug and/or the surgical procedure, and changes to concomitant medications will be captured at each study visit, as well as any unscheduled study visits that may occur.

6.4.1 6.1.4 Early Termination Visit

A patient may withdraw from the study at any time (see Section 7.3). If a patient is withdrawn, then every reasonable effort is to be made to complete the schedule of assessments described for the Early Termination Visit. A reason for the subject's withdrawal, if available, should be documented in the patient's medical notes and in the CRF.

6.4.2 6.1.5 Unscheduled Visit

At the Investigators discretion, a patient may attend for an unscheduled study visit. [redacted]

6.5 Discussion of Study Design and Choice of Control

This is an open label study, since both the Investigator and the patient are unmasked to the study procedure (i.e. subretinal injection). The study procedure involves a surgical intervention and therefore it is not ethically viable to have a masked surgical procedure performed. Male patients are chosen because choroideremia is an X-linked recessive disorder, which affects primarily males. Females are carriers of the disease. Some females may manifest a clinical phenotype similar to that seen in affected males, however, for the purpose of this study only males will be treated and followed up.

Since choroideremia is known generally to be a symmetrical disease, the fellow eye of affected sufferers can be utilized as an internal control for the study. The fellow eye will not receive any study treatment.

7 STUDY POPULATION

A total of 6 patients will be enrolled into the study. All patients must meet the following eligibility criteria for inclusion and exclusion:

7.1 Inclusion Criteria

1. Participant is willing and able to give informed consent for participation in the study.
2. Male aged 18 years or above.
3. Genetically confirmed diagnosis of choroideremia.
4. Active disease visible clinically within the macula region
5. Best-corrected visual acuity equal to or worse than 6/9 (20/32; Decimal 0.63; LogMAR 0.2) but better than or equal to 6/60 (20/200; Decimal 0.1; LogMAR 1.0) in the study eye.

7.2 Exclusion Criteria

1. Female and child participants (under the age of 18)
2. Participants with a history of amblyopia in the study eye
3. Men unwilling to use barrier contraception methods, if relevant
4. Grossly asymmetrical disease or other ocular morbidity which might confound use of the fellow eye as a long-term control
5. [redacted]Any other significant ocular and non-ocular disease/disorder [redacted]
6. Contraindication to use of medications or contrast agents [redacted]
7. Participants who have participated in another research study involving an investigational product in the past 12 weeks, or having had gene or cellular therapy at any time prior to this study.

7.3 Discontinuations

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant 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
- An adverse event which results in inability to continue to comply with study assessments
- Consent withdrawn

- Lost to follow up

Annual checks of general health and family planning will however need to be monitored continuously and every effort will be made to ensure that patients understand the need for this monitoring at consent. Withdrawal from the study will not necessarily result in exclusion of the data acquired up to the point of withdrawal. The reason for withdrawal will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilized.

8 STUDY TREATMENT

8.1 Treatments Administered

0.1ml of AAV2.REP1, containing 1 x 10^{11} genome particles, administered as a single subretinal injection.

There is no placebo or comparator product in this study. Since choroideremia affects both eyes in a generally symmetrical pattern, the fellow eye (which does not receive any study treatment) will be used as a comparator.

8.2 Method of Assignment to Treatment Eye

The study is open label. The treatment eye will be the worse eye, based on clinical examination. This will be discussed in detail and agreed with each patient as part of the informed consent process. Patient choice will be considered in cases where the degeneration is relatively symmetrical between the two eyes. Participants will also be reminded that they are free to withdraw consent at any stage.

8.3 Rationale for Dose Selection

Information is considered confidential.

[redacted]

8.4 Study Masking

This is an open label study with no masking. However, to minimize bias evaluation of the treated and non-treated eye, some assessments will be conducted by an appropriately qualified masked observer: Fundus Autoflourescence, Microperimetry, OCT, Visual Fields, Fundus Photography.

8.5 Concomitant Therapy

Details of concomitant medication will be collected at the screening visit, and updated at every study visit (including any unscheduled visits). Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. Any medication, (including anaesthetic and other surgical medications, but excluding study medication), taken during the study will be recorded in the patients' medical records and CRF.

8.6 Treatment Compliance

This is single subretinal injection of 0.1ml AAV2.REP1, containing 1 x 10^{11} genome particles. Treatment compliance measurement is unnecessary.

9 STUDY SCHEDULE

Information is considered confidential.

9.1 Efficacy Measures

Information is considered confidential.

9.2 Best Corrected Visual Acuity

Changes from baseline in visual acuity compared to the control eye is the study primary endpoint.

[redacted]

9.3 Fundus Autofluorescence

Changes from baseline in autofluorescence evaluation is a secondary efficacy endpoint.

[redacted]

9.4 Microperimetry

Changes from baseline in microperimetry readings is a secondary efficacy endpoint.

[redacted]

9.5 Optical Coherence Tomography (OCT)

OCT will be performed in both study and non-study eye [redacted]

9.6 Visual Fields

Conducted in both eyes [redacted]

9.7 Contrast Sensitivity

Contrast sensitivity will be measured in both eyes [redacted]

9.8 Color Vision

The Roth 28 test will be used. [redacted]

9.9 Safety Measure

9.9.1 Full Ophthalmic Examination

The full ophthalmic exam will be used as a safety assessment throughout the study [redacted] This examination will be conducted in both eyes. [redacted]

9.9.2 7-Field Color Fundus Photography

Conducted in both eyes [redacted]

9.9.3 Fluorescein and Indocyanine Angiography

Fluorescein and indocyanine angiography will be conducted in both eyes [redacted]

9.9.4 Vital Signs

Resting pulse and blood pressure will be taken. [redacted]

9.9.5 Blood Chemistry

Blood samples will be taken for urea, electrolytes and liver function tests. [redacted]

9.9.6 Viral Shedding

[redacted]

9.9.7 Immunogenicity

[redacted]

9.9.8 Adverse Events and Serious Adverse Events

Adverse events will be collected from the time the patient provides written informed consent for participation until the end of Visit 11 (and at ET and Unscheduled Visits, if appropriate). Patients will be questioned on the occurrence of an Adverse Event at every visit, by using non leading questioning such as 'how have you been seen the last visit?'.

9.9.8.1 Definition

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject, administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product or with the surgical procedure described in this protocol. When an AE is deemed to be related to a study drug, it may be termed as an Adverse Drug Reaction.

In order to standardize adverse event reports for analysis, the descriptions provided by patients and/or investigators will subsequently be coded into a standardized terminology by using the Medical Dictionary for Regulatory Activities (MedDRA). Other related variables like severity, outcome and relationship to investigational product or procedure will be captured in a standardized way in the Case Report Form.

Moreover, a number of events will be further characterized by the ophthalmic exams performed at each visit as part of the study procedures.

9.9.8.2 Serious adverse event (SAE)

A SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening*
- Requires inpatient hospitalization or prolongation of existing hospitalization**
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Visual loss or vision threatening
- Other important medical event(s)***

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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.

**Hospitalization for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.

*** Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.9.9 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure).

When determining the expectedness of an adverse reaction consideration should be given to:

- the underlying condition of the subject
- co-morbidity

- concomitant medications
- patient population
- severity and frequency of the occurrence

An unexpected adverse reaction meets one or more of the following criteria:

- not attributed to the underlying condition of the subject being studied
- not attributed to the patient population being studied
- not anticipated on the basis of prior experience with the drug under investigation or with related drugs
- not identified in the product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

9.9.10 Reporting and Recording of Adverse Events

Adverse events will be collected from the time the patient provides written informed consent for participation until the end of Visit 11 (or ET). Patients will be questioned on the occurrence of an Adverse Event at every visit including any unscheduled visit, by using non leading questioning such as 'how have you been seen the last visit?'.

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study medication or the surgical procedure, will be recorded in the CRF.

The following information will be recorded in the CRF for all AEs: 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 SAE definition). Follow-up information should be provided as necessary.

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: is not reasonably related in time to the administration of the Investigational Medicinal Product (IMP) or exposure of the IMP has not occurred.
- Unlikely to be Related: there are factors (evidence) explaining the occurrence of the event (e.g. progression of the underlying disease or concomitant medication more likely to be associated with the event) or a convincing alternative explanation for the event.
- Possibly Related: clinically or biologically reasonable relative to the administration of the IMP, but the event could have been due to another equally likely cause
- Probably Related: is clinically/biologically reasonable relative to the administration of the IMP, and the event is more likely explained by exposure to the IMP than by other factors and causes.
- Definitely related: a causal relationship of the onset of the event, relative to administration of the IMP and there is no other cause to explain the event.

AEs considered related to the study medication/study procedure as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

The relationship of AEs to the study medication will be assessed by a medically qualified investigator and discussed with the PI.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment (ET visit) and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

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)

Any pregnancy occurring during the clinical study and the outcome of the pregnancy fathered by trial participants, should be recorded and followed up for congenital abnormality or birth defect.

9.9.11 Reporting Procedures for Serious Adverse Events

The Data Monitoring Committee (DMC) will undertake to review all SAEs for the study. They may hold electronic meetings. The DMC will meet at intervals and consider:

- Occurrence and nature of adverse events
- Whether additional information on adverse events is required
- Consider taking appropriate action where necessary to halt trials (see below)
- Act / advise on incidents occurring between meetings that require rapid assessment (e.g. SUSARs)

All SAEs will be reported to the DMC within one day of discovery or notification of the event. All SAE information will be recorded on an SAE form which will be sent electronically to members of the DMC. Additional information received for a case (follow-up or corrections to the original case) will be detailed on a new SAE form.

The PI will also report all SUSARs to the Competent Authorities, Ethics Committee and any other governance body as required by local regulations. Fatal or life-threatening SUSARs will be reported within 7 days and all other SUSARs within 15 days. The PI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the PI shall submit once a year throughout the clinical trial or on request a safety report to the Competent Authority, Ethics Committee, and any other governance body as required by local regulations.

10 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.

Regular monitoring will be performed 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 clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

11 SAMPLE SIZE AND STATISTICAL METHODS

Information is considered confidential.

11.1 Determination of Sample Size

Six patients will be enrolled into this study. No formal sample size calculations have been performed.

11.2 Statistical and Analytical Plans

Information is considered confidential.
Summary statistics will be presented for both eyes (Treated Eye versus Control Eye groups). No formal statistical comparison will be performed (no p-value will be computed). For categorical/binary data, the number and proportion of patients pertaining to each category will be presented with its 95% Confidence Interval (CI). For continuous data, mean (and its 95% CI) and Standard Deviation (SD) will be presented.

12 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

12.1 Informed Consent

Choroideremia patients fulfilling the inclusion criteria who might be expected to benefit from gene therapy will be invited to take part in the study. Participants must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant 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 participant will be allowed as much time as wished 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 participant 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 Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site and an additional copy will remain in the patient medical records.

Independent counselling will be provided prior to acquiring signed informed consent. The following specific issues will be discussed:

1. The potential for no benefit
2. The potential for loss of vision due to complications of surgery, such as infection, retinal detachment, haemorrhage and cataract.
3. The potential for loss of vision due to immune reactions in the eye
4. The theoretical potential for malignancy spread of vector to other organs and germline transmission.
5. The nature and duration of follow-up tests required for the study.

The decision about which eye to treat will be made on clinical grounds and will generally be the worse eye affected. This will be discussed in detail and agreed with each patient as part of the informed consent process. Patient choice will be considered in cases where the degeneration is relatively symmetrical between the two eyes. Participants will also be reminded that they are free to withdraw consent at any stage.

12.2 Ethical Review

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee, regulatory authorities, and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.3 Regulatory Considerations

The study will be conducted in full conformity with all applicable law and regulations, including the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 2002.

13 ACCESS TO SOURCE DOCUMENTATION

Direct access will be granted to authorised representatives from the sponsor, host institution, NightstaRx Ltd and regulatory authorities to permit trial-related monitoring, audits and inspections.

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14 DATA HANDLING AND RECORDS MANAGEMENT

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. These electronic data entry systems have been validated. The participants will be identified by a study specific participants number and/or code in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

15 REFERENCE LIST

Bennicelli J, Wright JF, Komaromy A, et al. Reversal of blindness in animal models of leber congenital amaurosis using optimized AAV2-mediated gene transfer. Mol Ther. 2008;16(3):458-465.

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