GENE THERAPY TRIAL FOR LCA OPTIRPE65

An Open-label, Multi-Centre, Phase I/II Dose Escalation Trial of an Adeno-Associated Virus Vector (AAV2/5-OPTIRPE65) for Gene Therapy of Adults and Children with Retinal Dystrophy associated with Defects in *RPE65 (LCA2)*

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Authorisation: Chief Investigator

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Role	Chief Development Officer MeiraGTx UK II Ltd
Signature	
Date	26th June 2018

Table of Contents

1. Administrative information

This document was constructed using the MeiraGTx UK II Ltd. Protocol template. It describes the Gene Therapy Trial for LCA OPTIRPE65 trial, sponsored and co-ordinated by MeiraGTx UK II Ltd.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for ATIMP administration to other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial.

MeiraGTx UK II Ltd. supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials (Chan *et al*. 2013a). The SPIRIT Statement Explanation and Elaboration document (Chan *et al.* 2013b) can be referred to, or a member of MeiraGTx UK II Ltd. Clinical Operations team can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

MeiraGTx UK II Ltd. will be informed of any possible serious breach of compliance as soon as it is identified, so that the requirement to report the breach can be fulfilled within the relevant applicable timelines specified in each country in which the study is being conducted.

For the purposes of reporting, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants in the trial, or
- The scientific value of the trial.

1.2 Sponsor

MeiraGTx UK II Ltd., 92 Britannia Walk, London N1 7NQ is the study sponsor.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	Clinical trials.gov (NCT02781480)
Secondary Identifying Numbers	EudraCT: 2015-003418-25 Sponsor protocol number: MGT003
Source of Monetary or Material Support	Medical Research Council (MRC grant reference: MR/M015815/1) MeiraGTx UK II Ltd.
Sponsor	MeiraGTx UK II Ltd.
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Public Title	Gene Therapy Trial for LCA OPTIRPE65
Scientific Title	An Open-label, Multi-Centre, Phase I/II Dose Escalation Trial of an Adeno-Associated Virus Vector (AAV2/5-OPTIRPE65) for Gene Therapy of Adults and Children with Retinal Dystrophy associated with Defects in *RPE65* (LCA2)
Countries of Recruitment	United Kingdom, United States of America
Health Condition(s) or Problem(s) Studied	Retinal dystrophy associated with defects in *RPE65*
Intervention(s)	Open label, non-randomised, dose-escalation (low dose at 1.0 x10^{11} vg/mL; intermediate dose at 3.0 x10^{11} vg/mL; high dose at 1.0 x10^{12} vg/mL), phase I/II study, by subretinal administration of AAV2/5-OPTIRPE65 in up to 27 participants with LCA caused by mutations in *RPE65*.
Key Inclusion and Exclusion Criteria	Key Inclusion Criteria: • Aged 3 years or older • Early-onset severe retinal dystrophy consistent with *RPE65* deficiency • Homozygous or compound heterozygous missense or null mutations in *RPE65* • Functional or structural evidence of photoreceptor preservation • Able to undertake age-appropriate clinical assessments • Willing to give consent for the use of blood and blood components collected throughout the trial for the investigation of immune response to ATIMP Key Exclusion Criteria: • Females who are pregnant or breastfeeding • Contraindications for transient immune-suppression (i.e. history of diabetes mellitus, gastric or duodenal ulceration,

	hiatus hernia, uncontrolled gastro-oesophageal reflux in the past or are using non-steroidal anti-inflammatory drugs on a regular basis at the time of screening) Have participated in another research study involving an investigational therapy for ocular disease within the last 6 months. • Have had intraocular surgery within 6 months of screening. • Have an ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results
Study Type	Phase I/II, open-label, non-randomised, 2 centre, dose escalation in adults and children with retinal dystrophy associated with defects in *RPE65*
Date of First Enrolment	April 2016
Target Sample Size	Up to 27 participants
Primary Outcome(s)	The primary outcome is safety of subretinal administration of AAV2/5-OPTIRPE65. Safety is defined as the absence of ATIMP related: • reduction in visual acuity by 15 ETDRS letters or more • severe unresponsive inflammation • infective endophthalmitis • ocular malignancy • Grade III or above non-ocular SUSAR Safety will be assessed for 6 months after the intervention.
Key Secondary Outcomes	The secondary outcomes are measures of the efficacy of the intervention, which will be performed on an individual participant basis and will be descriptive in nature. 1) Any improvement in visual function from baseline that is greater that the test-retest variation for that test and is sustained for at least two consecutive assessments. 2) Any improvement in retinal function from pre intervention that is greater than the test-retest variation and measurable by electroretinography (ERG). 3) Quality of life measures

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

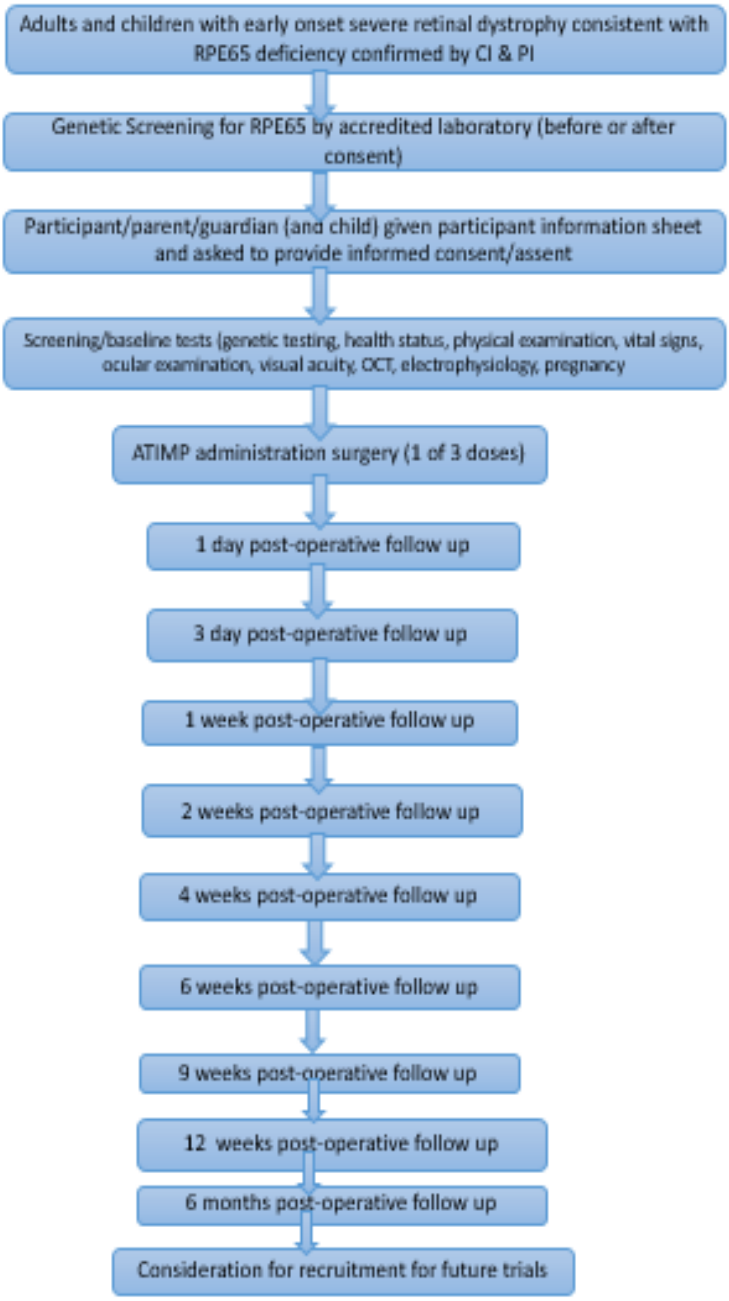
Name	Affiliation	Role
James Bainbridge	University College London	CI - Protocol development including surgical considerations
Michel Michaelides	University College London	Protocol development including clinical assessments

Stuart Naylor	MeiraGTx UK Ltd.	Protocol development
Julie Bakobaki	MeiraGTx UK Ltd.	Protocol development and co-ordination
Victoria McCudden	UCL CCTU	Clinical Project Manager
Simon Skene	UCL CCTU	Principal Statistician
Neruban Kumaran	University College London	Protocol development
Praseeda Thaikalloor	MeiraGTx UK Ltd	Protocol development and co-ordination

1.4.2 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Professor Hatice Nida Sen	National Institutes of Health	Independent Chair, Clinical Professor of Ophthalmology
Graeme MacLennan	University of Aberdeen	Independent statistician
Emma Morris	UCL Institute of Immunity and Transplantation	Independent member, Professor of Clinical Cell and Gene Therapy
Andrew Baker	University of Edinburgh	BHF Professor of Translational Cardiovascular Sciences

2 Trial Diagram



3 Abbreviations

AAV	Adeno-Associated Virus
Ad	Adenovirus
AE	Adverse Event
AF	Autofluorescence
AO	Adaptive Optics
AR	Adverse Reaction
ATIMP	Advanced Therapy Investigational Medicinal Product
bps	Basepairs
BGL65p	*hRPE65* promoter fragment that is less efficient than the NA65p promoter
CA	Competent Authority
CAI	Codon Adaptation Index
cDNA	complementary Deoxyribonucleic Acid
CLIA	Clinical Laboratory Improvement Amendments
CI	Chief Investigator
CMT	Clinical Management Team
CMV	Cytomegalovirus
CNS	Central nervous system
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
DAPI	4',6-diamidino-2-phenylindole
DLE	Dose-limiting event
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
EC	European Commission
eGFP	enhanced green fluorescent protein
ELISA	Enzyme-linked Immunosorbent Assay
ELISPOT	Enzyme-linked ImmunoSpot Assay
EMA	European Medicines Agency
EOSRDs	early-onset severe retinal dystrophies
EQ-5D-5L	EuroQOL Quality of Life 5 dimension 5 level
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FAF	Fundus Autofluorescence
FDA	(US) Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GFP	Green Fluorescent Protein
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GMSC	Genetic Modification Safety Committee
GTAC	Gene Therapy Advisory Committee
H&E	haematoxylin and eosin
HEK293T	human embryonic kidney epithelial cell line
hRPE65	human retinal pigment epithelium-specific

	protein 65 (all-*trans*-retinyl isomerase)
HSE	Health and Safety Executive
HTA	Human Tissue Authority
H2B	histone H2B
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Trial Number
ITRs	Inverted terminal repeats
ITT	Intention to Treat
IV (or iv)	Intravenously
IVI	Impact of Visual Impairment
KEC	Kellogg Eye Centre
LCA	Leber congenital amaurosis
LCA2	Retinal dystrophy associated with defects in *RPE65*
LREC	Local Research Ethics Committee
MA	Marketing authorisation
Main REC	Main Research Ethics Committee
mGMP	Manner-of-good manufacturing practice
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mRNA	Messenger RNA
NA65p	Optimised *hRPE65* promoter
NHS R&D	National Health Service Research & Development
NIH	National Institutes of Health
NIMP	Non Investigational Medicinal Product
NZW	New Zealand White
OBA	Office of Biotechnology Activities
OCT	Optical Coherence Tomography
ONL	Outer nuclear layer
PCT	Polymerase Chain Reaction
PERG	Pattern Electroretinogram
PHI	Protected Health Information
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
qds	quarter die sumendus (four times a day)
QOL	Quality of Life
QMMP	Quality Management and Monitoring Plan
qPCR	Quantitative Polymerase Chain Reaction
QP	Qualified Person for release of CTIMP
qPCR	Quantitative polymerase chain reaction

rAAV	Recombinant adeno associated virus
rAAV2/2	recombinant adeno-associated virus serotype 2
R&D	Research and Development
REC	Research Ethics Committee
RG	Research grade
RNA	Ribonucleic acid
RPE	Retinal Pigment Epithelium
RPE65	retinal pigment epithelium-specific protein 65 (all-*trans*-retinyl isomerase)
rt-PCR	reverse transcription- polymer ase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	standard deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Approval
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV40	Simian virus 40
TMF	Trial Master File
ToR	Terms of Reference
tRNA	Transfer ribonucleic acid
UAR	Unexpected Adverse Reaction
UCL	University College London
UCLH	University College London Hospital
UK	United Kingdom
US	United States of America
vg	Viral Genomes
WGTU	Wolfson Gene Therapy Unit
WT	Wild type

4 Introduction

4.1 Background and Rationale

4.1.1 Background

Inherited retinal degenerations cause sight impairment in approximately 1 in 3000 people in the Western world. There are currently no effective treatments. Leber congenital amaurosis (LCA) is a severe, early-onset form of inherited retinal degeneration involving both rod and cone photoreceptors (Perrault *et al*. 1999; Koenekoop, 2004). LCA is caused by mutations in one of at least 19 different genes (see https://sph.uth.edu/retnet). Mutations in *RPE65*, which is expressed in the retinal pigment epithelium (RPE), are responsible in 3 to 16 % of people affected. The *RPE65* gene encodes a 65-kDa retinal pigment epithelium (RPE)-specific protein that is required for the conversion of vitamin A to 11-*cis*-retinal by the RPE and is essential for the regeneration of the rod visual pigment (Hamel *et al*. 1993; Redmond*et al*. 2008). Mice and dogs that are homozygous for *RPE65* null mutations have abnormally low levels of 11-*cis*-retinal, resulting in very poor vision and depressed light- and dark-adapted electroretinogram responses (Ekesten *et al*. 2001; Dekomien *et al*. 2003). Children with *RPE65* mutations lack rod function from birth; residual cone function is typically extinguished by early adulthood (Marlhens *et al*. 1997; Cremers *et al*. 2002).

Proof-of-principle for *RPE65* gene replacement therapy has been demonstrated using recombinant adeno-associated virus serotype 2 (rAAV2/2) vectors in animal models (Acland *et al*. 2001; Acland *et al.* 2005; Jacobson *et al*. 2006; Le Meur *et al*. 2007; Bennicelli *et al*. 2008) of the condition and in 3 previous clinical trials (Bainbridge *et al.* 2008; Maguire *et al.* 2008; Cideciyan *et al.* 2008). In these 3 studies, adults and children as young as 6 years of age, were administered AAV vectors by sub-retinal administration at viral doses ranging from $1.5x10^{10}$ to $1x10^{12}$. Although vector administration was generally well-tolerated, a minority of participants who were administered 10^{12} viral genomes developed transient intraocular inflammation and immune responses to AAV indicating dose-limiting toxicity (Bainbridge *et al*. 2015). In all instances, intraocular inflammation resolved following more extended administration of corticosteroid treatment.

In all 3 clinical trials, subsets of participants benefitted with improved visual function to varying extents during the first year. However, longer-term follow-up demonstrated that progressive degeneration continued unabated, and the maximal improvements in retinal sensitivity were not maintained (Cideciyan *et al*. 2013; Bainbridge *et al*. 2015). Additional pre-clinical studies have shown that endogenous expression of *RPE65* in humans is greater than in the animal models, and support the hypothesis that continued degeneration reflects suboptimal *RPE65* expression in the human retina (Bainbridge *et al.* 2015).

To increase the availability of *RPE65* for affected humans we have developed a new optimized AAV vector. Having identified in our previous clinical trial the maximal tolerated AAV2/2 vector dose, we have optimized the therapeutic vector to drive more efficient transgene expression. We have achieved this by optimization of the construct and the Kozak sequence, inclusion of an exogenous intron, and

codon optimization. We will use an AAV2/5 vector to deliver the construct because we have determined that AAV2/5 vectors are more effective than AAV2/2 vectors for gene therapy in *Rpe65*-deficient mice. The aim of this trial is to determine the safety of this new optimised AAV2/5 vector in humans and to explore its potential efficacy.

4.1.2 Preclinical Data

Our new optimised vector, AAV2/5-OPTIRPE65, provides 300-fold greater efficacy in animal models compared with that used in our previous trial.

The toxicity of a single dose of AAV2/5-OPTIRPE65 administered as a subretinal injection has been evaluated in mice and rabbits. Long-term (9-month) overexpression of *RPE65* protein in the mouse RPE did not result in gross toxicity, as determined by clinical observations of health and behaviour or by increased mortality, or in ocular toxicity, as determined by functional and structural assessments of retinal health (Study RPE65-02/01). In 8-week single dose studies in mice (Study RPE65-02/02) and rabbits (Study RPE65-02/04), subretinal administration of AAV2/5-OPTIRPE65 did not result in local adverse effects on retinal structure or function. No overt systemic effects on health, as assessed by appearance or behaviour of the animals, or by macroscopic examination of the major organs post-mortem, were observed. Low level dissemination of vector to the liver, adrenal glands, and draining lymph nodes was detected in mice, and low level dissemination of vector to the liver and tissues of the optic tract was detected in rabbits. This low level dissemination of vector did not result in pathological changes. Subretinal administration of AAV2/-OPTIRPE65 in an *Rpe65*-deficient mouse strain did not result in adverse local or systemic effects (Study RPE65-02/03).

No immune responses against the *RPE65* protein were detected in a 4-week, single dose study of bilateral subretinal injection in the *Rpe65*-deficient (*Rpe65*$^{-/-}$) mouse Study (RPE65-02/03). There were some immune responses against the vector capsid in this study and in the 8-week single dose toxicity and biodistribution studies of AAV2/5-OPTIRPE65 in mice (Study RPE65-02/02) and rabbits (Study RPE65-02/04), as would be expected after administration of AAV vector. These were only detectable using the neutralising antibody assay. Anti-AAV5 immune responses were not more pronounced in the *Rpe65*-deficient (*Rpe65*$^{-/-}$) mouse compared with WT mice, and did not correlate with any changes in any of the other assessments.

4.1.3 Rationale

Inherited defects in the gene encoding *RPE65* cause night blindness and progressive loss of sight in children. There is currently no approved treatment available. In previous clinical trials we and others have shown that subretinal administration of recombinant AAV2/2 vectors containing the cDNA for human *RPE65* is generally well-tolerated and can improve low-luminance vision (night vision) in affected children and young adults (Bainbridge *et al*. 2008; Maguire *et al*. 2008; Cideciyan *et al*. 2008; Bainbridge *et al*. 2015). However, the efficacy of the intervention in humans is lower than that measured in mice and dogs with a similar condition. We hypothesise that higher efficacy can be achieved in affected humans by improving the efficiency of expression of *RPE65* through optimisation of the vector construct. The purpose of this trial is to determine whether administration of a new version of the

vector (AAV2/5-OPTRPE65), which has been optimised for efficiency of both transduction and *RPE65* protein production, is safe and can result in greater efficacy.

4.1.4 Risk/Benefit

A gene therapy trial in human volunteers should not put the participants at disproportionate risk and for this reason should be restricted to individuals with serious disorders where effective treatments are not available. Children with *RPE65* mutations lack rod function and night vision from birth; residual cone function and daylight vision is severely impaired by early adulthood. There is no established treatment. Although younger individuals in particular stand to benefit from gene supplementation therapy by virtue of their visual plasticity to accommodate an improvement in retinal function, we anticipate that people of a range of ages may benefit – as seen in the three aforementioned Phase 1 clinical trials. To define this range we will include participants of various ages in the trial; once an acceptable safety profile has been established in adults, we will include children. We will enhance the safety of the proposed approach by restricting transgene expression to the target tissue by virtue of rAAV vector tropism and the promoter sequence used, and by restricting the intervention to only one eye of each participant. The risk of adverse effects on foveal function will be further minimised by preferentially targeting the vector surgically to the extrafoveal retina.

4.1.5 Assessment and Management of Risk

The MHRA risk categorisation to participant safety in relation to the ATIMP is Type C (i.e. markedly higher than the risk of standard medical care). General risk management will include the detailed review of participants, appropriate intervals between ATIMP administration to successive participants, the dose escalation plan, and limiting the risks to children by initially demonstrating an acceptable safety profile in adults. In addition, the schedule of participants' assessments has been designed to identify the short-term and the long-term risks. Details of specific risks and their management strategies are outlined below.

4.1.5.1 Risk of immune responses to AAV capsid proteins or expressed RPE65 protein

There is a risk that inflammation will occur following intra-ocular administration of rAAV in participants. The risk of inflammation is likely to be highest during the early postoperative period after ATIMP administration, before vector capsids are degraded. The risk of inflammation during this period will be minimised by pre- and post-operative prophylactic administration of topical and systemic corticosteroids. In our first clinical trial of gene therapy, intra-ocular delivery of an AAV2/2 vector was followed by transient intraocular inflammation in 3 of 12 participants. In this current protocol, intraocular administration of an AAV2/5 has been well tolerated in the majority of participants to date. A minority of participants developed an episode of intraocular inflammation involving the posterior segment, which responded to further administration of systemic corticosteroids.

4.1.5.2 Risk of vector transmission to other organs

Biodistribution studies suggest that following subretinal injection of rAAV, there may be anterograde and trans-synaptic transport of small amounts of vector genome from the retina to central visual

structures (Stieger *et al*. 2008). This is likely to result from inadvertent transduction of retinal ganglion cells following reflux of vector into the vitreous. Since only tiny amounts of vector are likely to reach the brain, the possibility of transgene expression causing toxicity in the brain is likely to be very low.

4.1.5.3 Risks of insertional mutagenesis and oncogenesis

The possibility of oncogenic events due to vector-mediated insertional mutagenesis cannot be excluded with certainty, but available evidence suggests it to be unlikely given that (i) rAAV vector genomes integrate into host chromosomes at a very low frequency (Nowrouzi *et al.* 2012), (ii) a relatively low number of rAAV particles will be administered, and (iii) the eye predominantly contains non-dividing cells and consequently ocular tumours are very rare. Furthermore, oncogenesis has not been reported following injection of rAAV into thousands of rodent eyes. Even when we injected AAV vectors into a large number of tumour-prone *p53*$^{-/-}$ mice, we did not observe malignant transformation of retinal cells (Balaggan *et al*. 2012).

In the highly unlikely event that an intraocular tumour does arise in a participant, comprehensive monitoring procedures will enable early detection and thus prompt and appropriate management.

4.1.5.4 Risk of germline transmission

The risk of inadvertent germline transmission is very small. In a number of studies using a variety of animal models involving various routes of administration, including intraocular injection, inadvertent germline transmission by rAAV vectors has not been detected. Similarly, we detected no vector genomes in semen of participants in our previous retinal gene therapy clinical trial (Bainbridge *et al*. 2008). However, in a Phase I clinical trial where rAAV2 was used to deliver factor IX in participants with haemophilia B, vector sequences have been detected in semen samples, though not sperm, from 6 (of 7) participants for a short period after vector delivery (Manno *et al.* 2006). Although this indicates there may be some potential for inadvertent germline transmission following the systemic delivery of high doses of vector suspension, the possibility of such an event following the microsurgical delivery of tiny amounts of vector to intraocular compartments is considered to be remote. Participants who are fertile and sexually active will be requested to use double-barrier contraception for at least 12 months following ATIMP administration.

4.1.5.5 Risk of surgical adverse effects

The risk of significant surgical adverse effects is similar to the standard surgical care for other common forms of vitreo-retinal disorders. Only highly experienced surgeons will perform the procedure to limit the risk of surgical adverse events. These complications can normally be treated effectively by medication or further surgery and rarely result in a permanent effect on eyesight. The risk of permanent severe visual loss from vitrectomy surgery is approximately 1 in 1000. We have identified no significant surgical adverse effects in any of the 12 participants in our previous clinical trial performed using the same surgical procedure.

Delivery of vector suspension to the subretinal space will be performed following a standard surgical vitrectomy. This will involve a 3-port pars plana vitrectomy followed by injection of vector suspension using a fine cannula through small retinotomies, resulting in a transient retinal detachment. Previous

gene therapy clinical trials have shown that the bleb of subretinal vector suspension will resolve spontaneously over the course of the first 24 to 48 hours postoperatively as the fluid is absorbed by the underlying retinal pigment epithelium.

The aim of the intervention is to improve and/or to protect photoreceptor cell function. Previous trials have identified a risk of retinal thinning at the fovea, which is the site of greatest cone density, following subfoveal vector delivery. Although such thinning is not clearly associated with an adverse effect on foveal function in the short-term, we cannot exclude the possibility in the longer-term, and for this reason we aim to exclude the fovea from the area of vector delivery in the proposed trial.

Potential complications of surgery specifically include persistence of the subretinal vector bleb, the development of retinal tears, and persistent postoperative intraocular inflammation. We will minimise any risk to overall visual function by leaving the contralateral fellow eye untreated. Retinal detachment caused by persistent vector bleb or intraoperative retinal tear is expected to occur in fewer than 1 in 100 cases and can be effectively managed in the majority of participants by retinopexy with or without appropriate intraocular tamponade. Persistent intraocular inflammation will be managed by topical corticosteroid therapy with systemic steroids where indicated.

Vitrectomy surgery is a standard technique, commonly performed for a wide range of indications. Injection of fluids under the retina is less commonly performed but injection of Hartmann's solution (similar in composition to lactated Ringer's solution) is a standard step in surgery for macular degeneration.

4.1.5.6 Risk of adverse effects of short-term corticosteroids

Candidates will be screened to ensure there are no contra-indications for transient immune suppression by corticosteroids; in particular, a history of uncontrolled hypertension, diabetes mellitus, tuberculosis, renal impairment, osteoporosis, gastric ulceration, severe affective disorder and immunocompromised status. The possibility of steroid-induced adverse effects will be monitored regularly. In particular, blood pressure and blood glucose will be measured on Baseline, Day 1, Week 1, Week 2 and Week 4, as will renal function and liver function (at baseline and 1 day, 7 days, 2 weeks and 4 weeks and 6 weeks after surgery).

4.1.5.7 Risks of investigations performed during assessment and follow up

The majority of investigations are non-invasive routine clinical tests and present no significant risk. Venepuncture causes temporary discomfort, occasionally bruising/swelling and rarely infection at the site of puncture.

4.1.5.8 Conclusion on the risk-benefit ratio

In conclusion, the clinical benefit of delivery of the *RPE65* gene to the retinal epithelium was demonstrated in the clinical trial conducted with the first generation product (AAV2/2-hRPE65). Based on the specific modifications to that product (both regulatory elements that control gene expression, and sequences to enhance translation), it is hypothesised that AAV2/5-OPTIRPE65 will produce higher levels of RPE65 protein than AAV2/2-hRPE65, leading to greater improvements in visual function in

patients with LCA2. The investigators judge the scientific value of the trial and potential for individual participants to benefit outweigh the risks associated with the intervention.

4.1.6 Explanation for Choice of Comparators

There is no currently approved treatment for retinal dystrophy caused by mutations in *RPE65*, thus there are no comparators in this study. The contralateral fellow eye will be left untreated to minimize the risk to visual function and may also serve as a control.

4.2 Objectives

4.2.1 Primary Objective

The primary research objective is to assess the safety of a new optimised virus vector for RPE gene replacement in the retina. Safety is defined as an ATIMP related:

- Reduction in visual acuity by 15 ETDRS letters or more
- Severe unresponsive inflammation (defined below)
- Infective endophthalmitis)
- Ocular malignancy
- Grade III or above non-ocular SUSAR (See Section 5.11.3)

Classification of severe unresponsive inflammation will be according to the SUN (standardisation of uveitis nomenclature) Working Group grading system (Am J Ophthalmol. 2005 Sep;140(3):50916.) i.e

- anterior chamber cells 3+ (26-50 cells in a field size of 1mm x 1-mm slit-beam), or
- anterior chamber flare 3+ (marked, iris and lens details hazy) or
- vitreous haze 3+ (Ophthalmology 1985; 92:467-71)

that fail to improve by 2 steps (or to grade 0) during a 6 week period.

4.2.2 Secondary Objective

The secondary research objective is to determine whether a new optimised virus vector for *RPE65* gene replacement in the retina is effective at improving sight in terms of both visual and retinal function, and quality of life.

4.3 Trial Design

4.3.1 Overall Design

This is an open-label phase I/II dose-escalation trial to determine the safety and efficacy of a single subretinal administration of the ATIMP in participants with *RPE65*-related retinal dystrophy.

In the dose escalation phase, up to 18 adult participants will be administered one of 3 different doses of vector in cohorts of 3 participants at a time, using a 3+3 design. Based on toxicity data, the IDMC will

make a recommendation on the dose to administer to the next cohort of 3 participants. The IDMC may recommend additional participants be treated at a given dose before deciding how to proceed.

Adults are defined as participants aged 16+ in the UK and aged 18+ in the US.

Up to 9 children or adults (aged 3 or older) will then be included once an acceptable safety profile has been established in adults. The IDMC will agree the maximum tolerated dose in adults before recommending administering up to this dose in children.

Safety and efficacy will be assessed by clinical examination and special investigations according to the schedule in section 5.6 of the protocol for 6 months following the intervention.

4.3.1.1 Separate longer term follow up study

Participants will subsequently be invited to enrol in a separate 5-year follow-up study where they will be assessed for safety up to 60 months following ATIMP administration. The duration of long-term follow-up is therefore consistent with the recommendations of the current CHMP Guideline on Follow-up of Patients Administered with Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/60436/2007) of 22 October 2009, where it is stated that, for viral vectors without integration, latency or reactivation potential, a brief clinical history and sample testing should be performed pre-treatment, at 3, 6 and 12 months after treatment, and then yearly thereafter for a minimum of 5 years (and, if non-clinical tests or evidence from other clinical trials using identical vectors or modifications of vectors indicate a potential for integration or late re-activation, the monitoring should be extended to continue yearly after those 5 years until data indicate that there is no longer any risk to be followed). Further, although the FDA Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006) recommends a standard 15-year period of follow-up, it is also noted that a shorter period of follow up may be possible if the vector does not integrate and has no potential for latency and reactivation. The follow up study will be a non-intervention study designed to collect data on longer term safety and efficacy at the equivalent of 9, 12, 18, 24, 36, 48 and 60 months following ATIMP administration; as such, participants in both studies will be followed up more frequently than recommended in the guidance, as additional assessments following ATIMP administration are included in the initial study (at weeks 1, 2, 4, 6 and 9) and in the long-term follow up study (at months 9 and 18). The follow up study will be supported by a different source of funding, will have a separate protocol, participant information and consent processes, and will be submitted for separate ethical review. Participants in the current study will be encouraged to join the follow up study as part of their ongoing clinical review, but there will be no obligation on their part to do so. It is acknowledged that despite encouragement participants may choose not to participate in the long-term follow-up study; however, in this motivated population, where individuals are closely and regularly monitored by their specialist, this number is expected to be very small. Moreover, we anticipate that participants are more likely to join a long-term study at 6 months than at 2 years following intervention.

4.3.2 IMP administration Review and Dose Escalation Criteria and Process

Up to 18 adult participants (as defined in Section 4.3.1) will be administered 1 of 3 doses according to the dose-escalation criteria:

1) low dose 1mL at $1.0x10^{11}$ vg/mL
2) intermediate dose 1mL at $3.0x10^{11}$ vg/mL
3) high dose 1mL at $1.0x10^{12}$ vg/mL

Once a maximal tolerated dose is established, up to a further 9 participants aged 3 or above will continue to be administered vector up to the highest dose observed to be well tolerated in adults.

4.3.2.1 Dose escalation criteria and Dose Limiting Events

Dose escalation will be undertaken in adults, based on an escalation rule around Dose-Limiting Events (DLEs). An IDMC will review data from a minimum of 9 weeks of follow up from each cohort of 3 participants, before recommending the next dose to be assessed in a further cohort of participants.

A DLE is defined as any of the below occurring during the 9 weeks following administration, at least possibly related to the ATIMP, not surgery alone:

- Reduction in visual acuity by 15 ETDRS letters or more
- Severe unresponsive inflammation
- Infective endophthalmitis
- Ocular malignancy or
- Grade III or above non-ocular SUSAR (see section 5.11.3)

Severe unresponsive inflammation will be defined according to the Standardisation of Uveitis Nomenclature (SUN) Working Group grading system (Jabs *et Al.* 2005) i.e.

- anterior chamber cells 3+ (26-50 cells in a field size of 1mm x 1-mm slit-beam), or
- anterior chamber flare 3+ (marked, iris and lens details hazy), or
- vitreous haze 3+ (Ophthalmology 1985; 92:467-71)

that fails to improve by 2 steps (or to grade 0) during a 9-week period.

Review of safety data will be undertaken by the IDMC prior to each dose escalation. Children will be included at up to the highest safe vector dose recommended by the IDMC, once a safety profile has been established in adult participants.

4.3.2.2 Dosing process

4.3.2.2.1 Cohort 1

Vector will first be administered at the lowest dose to 1 adult participant only. This participant will be monitored for signs of toxicity for a period of 9 weeks. If there is no DLE as defined above after a minimum of 9 weeks, vector will continue to be administered at the same dose to 2 further adult participants. In the event of a DLE in the first adult in the cohort, a discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further adults. The IDMC will review the data collected on this cohort of participants up to 9 weeks following vector administration to the 3rd participant.

4.3.2.2.2 Cohort 2

In the event that there is no DLE in any participant, the IDMC will recommend administering vector at the intermediate dose level to a single adult participant. If there is no dose-limiting toxicity after a minimum of 9 weeks, vector will continue to be administered at the same dose to 2 further adult participants. In the event of a DLE in the first adult in the cohort, a discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further adults. The IDMC will again review the data available on this next cohort of adult participants up to 9 weeks following vector administration to the 3rd participant.

4.3.2.2.3 Cohort 3

In the event that there is no DLE in any participant, the IDMC will recommend administering vector at the highest dose level to a single adult participant. If there is no DLE after a minimum of 9 weeks, vector will be administered at the same dose to 2 further adult participants. In the event of a DLE in the first adult in the cohort, a discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further adults.

4.3.2.2.4 Additional considerations

In the event of a DLE in one of the 3 participants at any given dose, the cohort will be expanded at the same dose level. The IDMC will review the safety data and confirm that additional participants may be treated at this dose. The IDMC may recommend that the same dose of ATIMP is administered to additional participants. The dose escalation will continue until 3 participants have been either administered the highest dose without any DLEs, or until at least 2 participants among a cohort of 3 to 6 participants experience DLEs (i.e., ≥33% of participants with a DLE at that dose level), in which case the recommended dose will be the level below this toxic dose. In the event that 1 or 2 DLEs are seen at the first dose level, the IDMC may recommend administering a lower dose to that described in the protocol to a cohort of participants.

Table 1: Dose escalation table

Number of DLEs		**Action**	**Details**
Low dose			
Participants 1-3	**Participants 4-6**		
0/3		Increase	Give intermediate dose to next cohort of participants
1/3		Remain	Give low dose to another cohort of participants (Pt 4-6)
≥ 2/3		Stop	MTD not found. Consider lower dose
	≤ 1/6	Increase/stop	Has higher dose been tried? No: Give intermediate dose to next cohort of participants Yes: MTD found – low dose
	≥ 2/6	Stop	MTD not found. Consider lower dose
Intermediate dose			
Participants 1-3	**Participants 4-6**	**Action**	**Details**
0/3		Increase	Give high dose to next cohort of participants
1/3		Remain	Give intermediate dose to participants 4-6
≥ 2/3		Decrease/stop	Give low dose to 3 more participants. If 6 participants already had low dose, stop. MTD found – low dose.
	≤ 1/6	Increase/stop	Has higher dose been tried? No: Give high dose to participants 1-3 Yes: MTD found – intermediate dose
	≥ 2/6	Decrease/stop	Give low dose to participants 4-6. If 6 participants already had low dose, stop. MTD found – low dose
High dose			
Participants 1-3	**Participants 4-6**	**Action**	**Details**
0/3		Remain	MTD found – give high dose to participants in confirmation phase
1/3		Remain	Give high dose to participants 4-6
≥ 2/3		Decrease/stop	Give intermediate dose to participants 4-6. If 6 participants already had intermediate dose, stop. MTD found – intermediate dose
	1/6	Stop	MTD found – high dose
	≥ 2/6	Decrease/Stop	Give intermediate dose to participants 4-6. If 6 participants already had intermediate dose, stop. MTD found – intermediate dose

4.3.2.2.5 Confirmatory safety phase

MeiraGTx will seek IDMC agreement on the highest dose that can be administered in the expansion cohort. This may include up to 9 participants who may be adults or children. Recruitment into this expansion cohort can begin at any dose level up to the IDMC agreed highest dose level. Children are defined as those aged 15 and under in the UK and 17 and under in the US. Children will be administered up to the maximal tolerated dose identified in adults. Having identified a group of children who may be willing to participate in the study, the CI will prioritise ATIMP administration to older candidates in the first instance. The first child administered vector will be monitored for safety for a period of 9 weeks. If there is no adverse event consistent with the above definition of a DLE after a minimum of 9 weeks, vector will continue to be administered to up to 8 further participants. In the event of a DLE as described above in the first child, a discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further children.

5 Methods

5.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection.

5.1.1 Study Setting

The study settings are academic hospitals and academic research centres selected for their ability to perform the intervention and assessments required of this protocol. Participants will be recruited from 2 clinical centres: one in the United Kingdom (UK) and one in the United States (US). However, participants recruited from the centre in the US will have one clinical assessment performed at a separate centre so data will be collected from 3 centres: 1 in the United Kingdom and 2 in the United States of America.

5.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol and the ATIMP Investigator Brochure.

To participate in the Gene Therapy Trial for LCA OPTIRPE65, investigators and trial sites must fulfil a set of criteria that have been agreed by the Gene Therapy Trial for LCA OPTIRPE65Clinical Management Team (CMT) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants, enter data and collect samples
- Suitably trained and certified staff are available to undertake clinical assessments
- The site has access to all specialised equipment/devices needed for clinical assessments
- The site should be able to archive traceability data for a minimum of 30 years post expiry date of the ATIMP

- The site should have a pharmacy that is able to store, prepare and dispense ATIMP appropriately
- The site should be able to store, prepare, dispense, and administer ATIMP appropriately

Trial sites meeting eligibility criteria and that are accepted by the CMT as being suitable to recruit to the trial, will be issued with the Gene Therapy Trial for LCA OPTIRPE65 Trial Master File (TMF) documentation to use when applying for local approvals as applicable.

5.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a sponsor's Clinical Trial Site Agreement and an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, maintaining up to date GCP certification, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

5.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable volunteers within the agreed recruitment period (i.e. the investigator(s) regularly provide clinical care for the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

5.2 Site approval and activation

The regulatory authorisations for the trial requires that the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and US Food and Drug Administration (FDA) are supplied with the names and addresses of all participating site Principal Investigators. Clinical Operations staff at MeiraGTx UK II Ltd. will ensure this information is provided to both the MHRA and FDA.

On receipt of the signed Clinical Trial Agreement and Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any participants until a letter for activation has been issued.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the competent authorities, and which was given favourable opinion by the UK Research Ethics Committee (REC) and local Institutional Review Board (IRB) in the US. The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the clinical operations team at MeiraGTx UK II Ltd.

5.3 Participants

5.3.1 Eligibility Criteria

5.3.1.1 Participant selection

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety, and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

The trial CI will confirm the eligibility of all individual participants.

5.3.1.2 Participant Inclusion Criteria

Inclusion in the trial will be limited to individuals who:

1. Are aged 3 years or older (although children, as defined in Section 4.3.2.2.5 will only be enrolled once the MTD has been agreed)
2. Have early-onset severe retinal dystrophy consistent with *RPE65* deficiency
3. Have homozygous or compound heterozygous missense or null mutations in *RPE65* confirmed in an accredited laboratory
4. Have functional or structural evidence of photoreceptor preservation as assessed by static perimetry (for visual field assessment) and SD-OCT scanning respectively*
5. Are able to give informed consent or assent, with the guidance of their parent/guardian where appropriate: children aged 3-6 years will not be asked to provide assent.
6. Are able to undertake age-appropriate clinical assessments at the trial sites as specified in the protocol
7. If female and of child bearing potential, are willing to use an effective form of birth control (hormonal or barrier method of birth control; or abstinence) for at least 12 months following ATIMP administration;
8. If male, are willing to use barrier and spermicide form of contraceptive or maintain sexual abstinence for 12 months following ATIMP administration
9. Females of childbearing potential will have a negative pregnancy test on the day of ATIMP administration. Participants are considered not of childbearing potential if they are pre-pubescent, surgically sterile (i.e. they have undergone a hysterectomy or bilateral oophorectomy) or post-menopausal
10. Are willing to give consent for the use of blood and blood components collected throughout the trial for the investigation of immune responses to the ATIMP

*if the tests having been performed within the 3 months of enrolment and the subject has consented to allow the use of those test results, then these tests will not need to be repeated.

5.3.1.3 Participant Exclusion Criteria

Individuals will be excluded who:

1. Are females who are pregnant or breastfeeding
2. Have contraindications for transient immune-suppression by systemic corticosteroids (including uncontrolled hypertension, diabetes mellitus, tuberculosis, renal impairment, osteoporosis, gastric ulceration, severe affective disorder) or are immunocompromised
3. Have a previous (within 5 years) history of gastric or duodenal ulceration, hiatus hernia, uncontrolled gastro-oesophageal reflux or are using non-steroidal anti-inflammatory drugs on a regular basis at the time of screening
4. Have a known allergy to any of the non-investigational drugs to be used in the trial as defined in Section 5.4.1
5. Have participated in another research study involving an investigational medicinal therapy for ocular disease within the last 6 months
6. Have any other condition that the PI considers makes them inappropriate for entry into the trial
7. Have had intraocular surgery within 6 months of screening
8. Have an ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results
9. Are unwilling to consider the possibility of entry into a subsequent longer term follow up study

5.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

Individuals performing the interventions will be limited to those qualified by training and experience to perform those interventions.

Surgery will only be performed by a qualified vitreo-retinal surgeon. The ATIMP will be administered by designated individuals at each study site to promote consistency of the intervention. The CI has developed a training programme that involves any designated individuals being trained in person by the CI. This may involve observations of the procedure being performed in the UK or the US. The completion of this training is one of the criteria that will be satisfied prior to site activation.

5.3.1.5 Co-enrolment Guidance

Individuals who have participated in another research study involving an investigational medicinal therapy for ocular disease within the last 6 months, will not be eligible for enrolment in this study.

5.3.1.6 Screening Procedures

Written informed consent to enter into the trial must be obtained from participants, or parents/guardians/person with legal responsibility (including legal authorities) for children, after explanation of the aims, methods, possible benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial. The only procedures that may be performed in advance of written informed consent being obtained are those that would be

performed on all individuals in the same situation as a usual standard of care. Data obtained previously from subjects enrolled on the MGT005 LCA Natural history study may be used for screening and/ or baseline assessments if testing was performed within the screening/baseline window of this trial and the subjects have provided informed consent for the use of the prior obtained results.

5.3.1.6.1 Informed Consent Procedure

Written informed consent will be taken from each participant (or parent/guardian if the participant is a child) by the chief/principal investigator or delegated clinician following appropriate explanation of the aims, methods, possible benefits and risks of the study. The Investigator or designee will explain that the participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason, and without their clinical care being affected. No clinical trial procedure will be conducted prior to taking consent from the participant.

The consent process will be managed during at least 2 meetings. At an initial meeting, information will be presented to potential participants in a form appropriate to their level of understanding. In the case of children, they and their legal guardian(s) will be offered the support of a family support counsellor (in the UK) or genetic counsellor (in the US). Potential participants will be provided with the relevant participant information sheets (or audio versions) and given time (a minimum of 24 hours) to consider their decision.

At a subsequent meeting, potential participants will be provided with a further opportunity to ask questions and to sign the consent form. Children will be invited to give their verbal (and noted in their medical notes) or written assent to participation where this is age appropriate (i.e. children aged over 6 years). Where children aged over 6 years do not assent, they will not be entered into the trial. A copy of the signed Informed Consent form will be provided to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

If new safety information results in significant changes in the risk/benefit assessment, the participant information sheet and consent form will be reviewed and updated if necessary, and participants will be re-consented as appropriate.

Children who become of adult age (i.e. 16 in the EU, 18 in the US) during the study will be reconsented as adults at the time of their next visit.

5.3.1.6.2 Screening Period

Screening procedures will take place only after the informed consent form has been signed by the participant/parent/guardian. However, if test results are available from the subject's participation in the MGT005 LCA natural history study, and the subject has consented to allow the use of those test results, then those screening tests will not need to be repeated.

Participants will undergo genetic screening for *RPE65* mutations at an accredited laboratory prior to enrolment.

Participants will be screened to ensure there are no contra-indications for transient immune suppression, in particular: hypertension, diabetes mellitus, tuberculosis, renal impairment, immunocompromised status, osteoporosis, gastric ulceration or severe affective disorder.

Screening assessments are listed below (and set out under the column headed 'Screening' in the Trial Assessments Table 2, Section 5.6):

1. Genetic testing
2. Medical history and concomitant medication
3. Physical examination
4. Vital signs (including height and weight)
5. Ocular examination
6. Visual acuity
7. Contrast Sensitivity
8. Spectral Domain Optical Coherence Tomography (SD-OCT) imaging depending on age, as a greater degree of co-operation is needed compared to SD-OCT)
9. Electrophysiological assessment

A letter from the general practitioner detailing the health status of the participant may be requested if the clinician deems it appropriate to confirm eligibility for the trial.

These assessments must have been completed within 3 months prior to enrolment. In addition, females of child bearing potential will undergo a pregnancy test at screening and again on the day of ATIMP administration.

5.3.1.6.3 Enrolment

Participants who fulfil the inclusion criteria based on the results of all screening assessments and pregnancy test will be enrolled in the trial. The ATIMP will be administered within 3 months of enrolment. If the ATIMP is not delivered within 3 months of enrolment, all screening tests with the exception of genetic testing and electrophysiological assessment will be repeated and eligibility for enrolment re-assessed.

Participants who withdraw or are withdrawn from the study for any reason prior to ATIMP administration may be substituted in the study.

5.4 Interventions

5.4.1 Products

5.4.1.1 Name and Description of Investigational Medicinal Product(s)

AAV2/5-OPTIRPE65 is an advanced therapy investigational medicinal product; specifically, a gene therapy product.

It consists of a linear single strand of DNA packaged in a recombinant adenovirus-associated virus (rAAV) protein capsid of serotype 5. The rAAV.hRPE65p.hRPE65 incorporates the wild-type AAV inverted terminal repeats that provide the packaging signal, a cDNA encoding human *RPE65*, the human *RPE65* promoter, a SV40 intron sequence, and a SV40 polyadenylation signal. The icosahedral capsid consists of three related AAV5 capsid proteins, VP1, VP2, and VP3. AAV has a compact macromolecular structure and forms stable viral particles approximately 20 nm in diameter. The vector particles are replication-incompetent.

RPE65 is an isomerase expressed in the retinal pigment epithelium (RPE) that catalyses the isomerization of all-trans-retinyl esters to 11-*cis*-vitamin A, and is a critical component of the visual biochemical cycle that regenerates visual pigment after light exposure. The lack of functional *RPE65* leads to a deficiency in 11-*cis*-retinal, the light-sensitive chromophore that binds to opsin, and results in diminished rod photoreceptor function. Recombinant AAV-mediated gene transfer of a normal *RPE65* gene to the RPE leads to stable, long-term transgene expression and improves visual function in rodent and dog models of disease. The study agent is based on the virus vector that led to improved night vision in a previous clinical trial (Bainbridge *et al*. 2008, Bainbridge *et al*. 2015); the original configuration has been modified to improve efficiency of *RPE65* gene expression at least 300-fold.

5.4.1.2 ATIMPs Classified as Genetically Modified Organisms

The ATIMP (AAV2/5-OPTIRPE65) is classified as a genetically modified organism under the Genetically Modified Organisms (Contained Use) Regulations 2000.

The Health and Safety Executive (HSE) must be notified of each UK clinical trial site administering the ATIMP for first use of premises for genetic modification activities before the activities commence. A risk assessment of the activities has been carried out and has been reviewed by the local Genetic Modification Safety Committee (GMSC). Internal approval at site for the GMO activities has been gained.

Each clinical trial site administering the ATIMP in the US must obtain local Institutional Biosafety Committee approval to administer recombinant nucleic acid molecule material to human subjects. Trial sites that receive support for recombinant or synthetic nucleic acid molecule research from the National Institutes of Health (NIH) must submit the protocol to the NIH Office of Biotechnology Activities (OBA) for review prior to initiating trial activities.

5.4.1.3 Source of ATIMPs

The ATIMP has been manufactured at the Wolfson Gene Therapy Unit (WGTU) facility of the UCL Gene Therapy Consortium at the UCL Cancer Institute in accordance with current Good Manufacturing Practice for clinical trial materials. The manufacturer will perform analytical testing and provide QP certification for release.

5.4.1.4 Preparation and Labelling of the Investigational Medicinal Product

Preparation and labelling of the investigational medicinal product will be completed in accordance with the relevant GMP guidelines and MeiraGTx UK II Ltd. procedures.

The ATIMP is a recombinant serotype 2/5 adeno-associated viral vector containing a human *RPE65* cDNA driven by a fragment of the human *RPE65* promoter. The manufacturer (WGTU) will perform analytical testing and provide QP certification for release. Aliquoting into vials and labelling of the ATIMP is the responsibility of WGTU. The WGTU is also responsible for testing, QP release and storage of the final ATIMP. Performance of certain release assays is contracted to approved contractors of the WGTU.

US Federal regulations require that a drug should be the subject of an approved marketing application before it is transported or distributed across state lines. As such, in order to ship INDs to investigators, the sponsor will submit an IND application in order to obtain an exemption from the FDA with regard to the marketing approval requirement.

5.4.1.5 Description and Justification of Route of Administration and Dose

Efficient transduction of the target retinal pigment epithelial cells requires the ATIMP (AAV2/5-OPTIRPE65) to be administered to the subretinal space. Delivery of vector suspension to the subretinal space will be performed following a standard surgical vitrectomy. This will involve a 3-port pars plana vitrectomy followed by injection of vector suspension using a fine cannula through 1 or more small retinotomies into the subretinal space, resulting in temporary retinal detachment. Previous gene therapy clinical trials have shown that the bleb of subretinal vector suspension can be expected to resolve spontaneously over the course of the first 24 to 48 hours postoperatively as the fluid is absorbed by the underlying retinal pigment epithelium. Risks to visual function will be minimized by controlling the area of vector delivery, and by leaving the contralateral fellow eye untreated. Vitrectomy surgery is a standard technique, commonly performed for a wide range of indications. Injection of fluids under the retina is less commonly performed but is a standard step for delivery of surgical dyes and therapeutic thrombolytic agents to the subretinal space.

Comparative experiments in *Rpe65*-deficient mice have shown that AAV2/5-OPTIRPE65 is 300-fold more potent than the AAV2/2-hRPE65 vector used previously. Given that AAV2/5-OPTIRPE65 is at least 300 fold more potent in mouse rescue experiment than AAV2/2-hRPE65, administration of 1×10^{11} vg/eye of AAV2/5-OPTIRPE65 would thus result in an approximately 30-fold increase in effective *RPE65* delivery compared with that resulting from administration of 1×10^{12} vg/eye of AAV2/2-hRPE65 (rAAV2/2.hRPE65p.hRPE65) in the first clinical study (10-fold lower dose of a vector that is 300-fold more potent). In addition, as a 7-fold more efficient translation is seen with the optimized vector in human cells, it is possible that greater improvements in ERG and retinal survival may be observed at the proposed starting dose. Importantly, based on existing knowledge, it is not anticipated that this enhanced translation efficiency and potency of the vector would be detrimental to the patients. This approach is intended to maximize potential benefit for patients participating in the study by commencing dosing at a level that is theoretically effective.

The intended administration volume of 1mL is considered appropriate to enable optimal exposure of target RPE cells to the vector, even in young children. The location of retinotomies will be determined with the aim of exposing those RPE cells that support overlying viable photoreceptor cells as determined by optical imaging. Whilst the surgical technique is designed to optimise the possibility of benefit, any

concern arising intra-operatively about possible adverse events will be appropriately addressed in the interests of safety, and any deviations from protocol recorded.

5.4.1.6 Name and Description of Each Non-Investigational Medicinal Drug (NIMP)

1. Cefuroxime or cefazolin or vancomycin antibiotic given at usual dose at end of surgery (standard dose as prophylaxis for post-operative infection)

2. Betamethasone or dexamethasone given at usual dose at end of surgery (standard dose as prophylaxis for post-operative inflammation)

3. Chloramphenicol 0.5% or ofloxacin (topical antibiotic) 4 times daily for 7 days following ATIMP administration

4. Dexamethasone 0.1% (topical steroid) 4 times daily for 4 weeks, then 2 times daily for a further 2 weeks (weeks 4 to 6) following ATIMP administration

3 and 4 above will be administered to minimise inflammation and protect against infection postoperatively.

5. Omeprazole:

- In adults 20mg per day for 8 weeks
- In children weighing 5 kg to less than 10 kg (11 lb to less than 22 lb): 5 mg taken once per day
- In children weighing 10 kg to less than 20 kg (22 lb to less than 44 lb): 10 mg taken once per day
  In children weighing 20 kg (44 lb) or more: 20 mg taken once per day

6. Prednisolone or Prednisone (oral steroid) as prophylaxis against potential intraocular immune responses:

For adults 30 mg daily for one week **prior** to ATIMP administration

Following the ATIMP administration as follows:

- 60 mg daily in week 1
- 40 mg daily in week 2
- 30 mg daily in week 3
- 20 mg daily in week 4
- 15 mg daily in week 5
- 10 mg daily in week 6
- 5 mg daily in week 7
- 2.5 mg daily in week 8

Children will be prescribed a tapering regimen of prednisolone tailored according to age and weight, and in addition intravenous methylprednisolone 30mg/kg on the day of surgery (maximum total no more

than 1g). A further dose of methylprednisolone may be administered at week 4 in the presence of signs of intraocular inflammation. The detailed treatment regimen is described in a clinical management plan.

All Non Investigational Medicinal Products (NIMPs) are licensed within the EU and US and will be procured from standard hospital stock.

Sites will maintain a system that allows adequate reconstruction of NIMP movements and permits recording of which participants received which NIMPs during the trial, with an evaluation of the compliance where necessary.

5.4.2 Protocol defined clinical schedule

5.4.2.1 Baseline Assessments

Assessment of visual function and retinal imaging of both eyes will be performed preoperatively as outlined in Section 5.6 (Table 2, Trial Assessments). For assessments requiring multiple baselines, testing is preferred on separate days within a maximum 3-month period to allow for day to day variation and test retest variability for individual participants. However, it is acknowledged that a balance will be achieved between what is pragmatic and appropriate for the different tests on an individual basis. Each set of baseline measurements may take up to 3 days to perform in total. In some instances, results for protocol specified baseline tests may be available through a subject's prior participation on the MGT005 LCA natural history study. As such, if the subject provides informed consent to use the results from the previously conducted tests, then these assessments will not need to be repeated at baseline.

Visual assessments results will be sent for reading and analysis to independent reading centres within the UK and US. For both sites Imaging for OCT and Fundus photography will be reviewed by the site teams but also sent for independent analysis by the Reading Centre, Queens University, Belfast during the course of the trial. Adaptive optics images will be sent to the Medical College of Wisconsin for reading and Octopus perimetry and Microperimetry will be sent to the Oregon Health and Science University Casey Eye Institute reading centre. All images will be saved under pseudo anonymised patient identifiers and images will only be taken of the patient's eye to ensure that patients will remain unidentified.

Up to 10 mL of blood will be sampled in order to assess baseline levels of T-cell responses to AAV5 and of circulating antibodies against AAV serotype 5 and *RPE65* so that immunological responses to vector capsids and transgene product might be determined following vector administration (collectively described as serology in Table 2, Trial A assessments). We anticipate that the majority of participants will have no detectable pre-existing circulating antibodies against AAV5 or *RPE65*. The presence or absence of circulating antibodies will not affect recruitment of the participant. All serology tests will be carried out at the sponsor's approved Laboratory in the UK.

There is wide variability in the ability of children of different ages to undertake some of the proposed tests; the evaluations for children will be restricted to those tests that they are able to perform reliably.

Tests that will be performed in all participants are:

1. Serological tests
2. Blood pressure
3. Haematology
4. Biochemistry
5. Ocular examination
6. Intraocular pressure
7. Colour fundus photography
8. Spectral Domain Optical coherence tomography (SD-OCT)
9. Fundus Autofluorescence imaging (FAF)
10. Best corrected visual acuity
11. Full-field electroretinography (ERG)
12. Pattern electroretinography (PERG)

Tests that will be performed where possible are:

13. Contrast sensitivity
14. Reading assessment
15. Colour vision testing
16. Microperimetry (mesopic and scotopic)
17. Octopus900 full-field static perimetry
18. Vision-guided mobility
19. Multifocal electroretinography (mfERG)
20. Adaptive optics (AO) imaging
21. QOL questionnaires

Further details of clinical assessments can be found in the OPTIRPE65 study manual.

(i) Ocular examination and retinal imaging

Ocular examination by slit lamp biomicroscopy will be used to assess the anatomical integrity of the eyes and quantify any intraocular inflammation. During the examination, intraocular pressure will be determined by tonometry.

Retinal imaging includes colour fundus photography (ETDRS 7 standard fields), FAF, SD-OCT, and AO imaging. FAF imaging allows visualisation of the retinal pigment epithelium (RPE) by taking advantage of its intrinsic fluorescence derived from its lipofuscin content. SD-OCT imaging enables measurement of retinal thickness and provides information about the integrity of the layers of the retina. AO imaging provides direct visualization of the photoreceptor and RPE mosaics *in vivo.*

(ii) Functional and Participant-Related Outcome assessments

Where possible the participant will complete an age-appropriate Impact of Visual Impairment (IVI) vision-specific quality of life questionnaire, and EQ5D-5L and EQ-5D-Y questionnaires.

Reading ability, including reading acuity, maximum reading rate, and critical print size will be assessed with MNRead and International Reading Speed Texts.

Best-corrected ETDRS visual acuity will be measured in each eye. Contrast sensitivity will be measured using the Pelli-Robson chart.

Colour vision testing will be undertaken using plate tests and computerised tests probing colour discrimination.

Retinal sensitivity will be determined using Octopus 900 full-field static perimetry and/or full field stimulus testing (FST) where available, and microperimetry (mesopic and scotopic). Where available, FST may be performed for enrolled paediatric patients at participating sites. The retinal locus of fixation will also be accurately determined using microperimetry.

Vision-guided mobility will be assessed by measuring the ability of each participant to navigate a simple route in a range of controlled illuminances.

Full-field electroretinography (ERG), pattern ERG (PERG) and multifocal ERG (mfERG) will be performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards to assess both generalised retinal (RPE, rod and cone systems) and isolated macular function. Modified ISCEV protocols may be necessary in young children using internationally recognised modified protocols. For young children, this procedure may be performed under general anaesthesia. ERG data will be analysed and interpreted by dedicated full-time Clinical Visual Electrophysiology Consultants with extensive experience and who are directly involved in determining ISCEV standards.

5.4.2.2 ATIMP administration Procedures

The ATIMP administration procedures described in the protocol are what is broadly intended to occur during surgery. Anticipated procedures may be modified on a case-by-case basis in the interests of safety, and these modifications will be documented in the operation notes and CRF. Consent to record the surgery will be requested of the participant. Intraocular surgery will be recorded using a video camera via the operating microscope. Relevant recordings and images will be stored alongside the trial database.

5.4.2.2.1 Preoperative procedure

For prophylaxis against potential intraocular immune responses to the ATIMP, participants will be prescribed a course of daily oral prednisolone (or other as appropriate) commencing at a dose of 30mg daily for 1 week prior to ATIMP administration.

Preoperative procedures and intraocular administration of ATIMP will be as described in the OPTIRPE65 study manual

5.4.2.2.2 Operative procedure

The choice of eye that the vector is delivered to will be made between the participant and PI. It is anticipated that this will be the poorer-seeing eye but this will be decided upon in discussion with the participant.

The recombinant vector will be delivered in the form of a suspension of viral vector particles injected intraocularly (subretinally) under direct observation using an operating microscope. This procedure will involve 3-port pars plana vitrectomy followed by injection of vector suspension using a fine cannula through 1 or more small retinotomies into the subretinal space. The procedure may be performed under general or local anaesthesia at the discretion of the operating surgeon and the participant.

The eye and face will be prepared using povidone iodine solution. The face and eye will be covered with an adhesive sterile plastic drape. An opening will be made at the point of the palpebral fissure and a wire speculum inserted to retract the upper and lower eyelids. The speculum and all intraocular instruments will be sterilised according to standard local operating procedures. An intraocular infusion cannula will be placed to maintain a normal globe volume by infusion of fluid. 2 further pars plana sclerotomies will be placed to accommodate an endo-illumination probe and vitreous cutter. The fundus will be viewed by means of a BIOM indirect viewing system or a contact lens. The posterior hyaloid will be peeled anteriorly and the vitrectomy completed using the vitreous cutter.

The specific area of retina to be targeted in each participant will be pre-determined according to the degree and distribution of retinal degeneration defined by pre-operative assessments. Intraocular administration of the viral vector suspension (AAV2/5-OPTIRPE65) will be performed using a cannula attached to a syringe. The cannula will be advanced through the retina at sites pre-determined in each participant according to the area of retina to be targeted. Where possible, the vector will be targeted to exclude the fovea. If appropriate, the bleb of vector may be manipulated to the target area using a fluid-air exchange. Under direct visualisation the vector suspension (1.0×10^{11} to 1.4×10^{12} vg/mL; up to a maximum volume of 1 mL) will be injected under the neurosensory retina causing a localised retinal detachment. The first 3 adult participants will receive the low dose (1.0×10^{11} vg/mL), with 3 subsequent adults receiving the intermediate dose (3.0×10^{11} vg/mL) and 3 subsequent adults receiving the high dose (1.0×10^{12} vg/mL) according to the dose-escalation criteria. Children will be included only after safety has been appropriately determined in adults. The injection of vector suspension may be preceded by injection of a small volume of saline solution (0.1 to 0.5 mL) to establish a “bleb” facilitating targeted delivery of vector suspension to the subretinal space and minimising possible exposure of the choroid and vitreous cavity to vector. The injection retinotomy is designed to be self-sealing with minimal reflux. Following administration of vector suspension, the area of the induced retinal detachment will be documented by fundus photography.

On the basis of the findings of previous clinical studies, it is predicted that retinal blebs (localised retinal detachments) generated by subretinal vector delivery will resolve spontaneously with retinal re-attachment during the first 48 hours, without the need for retinopexy or intraocular tamponade. However, any unplanned peripheral retinal breaks will be managed appropriately using cryo- or laser-retinopexy and injection of an appropriate tamponade agent at the time of surgery, or as part of a

subsequent procedure. Sclerotomies may be closed using sutures at the surgeon's discretion. Standard doses of cefuroxime antibiotic and betamethasone or their equivalent will be administered subconjunctivally as prophylaxis against postoperative infection and inflammation respectively. The operated eye will be dressed with a pad and shield.

5.4.2.3 Subsequent Assessments

Surgery may be performed, as is conventional for intra-ocular procedures, on a day-case basis. Participants will subsequently be managed as outpatients, though hospital-based accommodation may be used for convenience.

On the first postoperative day a clinical ocular examination will be performed. In particular, visual acuity, intraocular pressure, any postoperative intraocular inflammation and the area of any residual retinal bleb will be documented. Fundus photography and SD-OCT scanning will be performed on the day 1 and subsequent assessments.

A standard post-vitrectomy treatment regimen of topical antibiotic (e.g., chloramphenicol 0.5% qds for 7 days), and corticosteroid (e.g. dexamethasone 0.1% qds for 4 weeks and then bd for a further 2 weeks) will be commenced to minimise inflammation and protect against infection postoperatively. Intraocular pressure of greater than 30 mmHg will be managed using appropriate ocular antihypertensive therapy.

Participants will be maintained on oral prednisolone (or other as appropriate) for 8 weeks following administration of vector suspension as described above (Section 5.4.2.2, Preoperative procedure). The possible development of steroid-induced adverse effects will be monitored regularly. In particular, blood pressure, blood glucose, renal function and liver function will be measured.

Female participants of childbearing potential and male participants with partners of childbearing potential will be advised to use a double barrier method of contraception for 12 months after surgery.

Both safety and efficacy of the ATIMP will be evaluated at various time points up to 6 months after ATIMP delivery. Evaluation will occur primarily by ocular assessments. The nature and schedule (Section 5.6, Study assessments) of these is described below.

Participants will subsequently be invited to enrol in a 5-year follow-up study to determine longer term safety and efficacy.

(i) Clinical assessment of intraocular inflammation

The degree of intraocular inflammation will be assessed by slit-lamp biomicroscopy at each time point. A temporary intraocular inflammatory response is predictable following vitrectomy surgery. This is typically evident clinically on slit lamp biomicroscopy as 'flare' and cells in the anterior chamber and can be of moderate (2+) intensity. The degree of intraocular inflammation is expected to decline during the course of the first 8 weeks following the surgical procedure at which time the routine topical and systemic immunosuppression will be discontinued. Prolonged or recurrent intraocular inflammation will be managed conventionally by further topical and/or systemic immunosuppression.

(ii) Evaluation of immune responses

Up to 10mL of blood will be sampled to measure immune response. Blood serum will be isolated and analysed. Residual samples will be stored in an approved laboratory designated by the sponsor for use in future ethically approved research, with the participant's consent. Immunological assays will be performed as outlined in Section 5.6 (Trial Assessments) to investigate antibody responses to AAV capsid proteins and to RPE65 protein. Investigators performing these analyses will be masked to participant's identity.

(iii) Evaluation of biodistribution

Systemic biodistribution of vector genomes will be assessed at as outlined in Section 5.6 (Trial Assessments) by PCR analysis of tears from the study eye (a compressed cellulose sponge placed under the eye lid until swollen), saliva (a minimum of 100 µL) and serum (100 µL). This test will be carried out in the institutional laboratory in the UK.

(iv) Assessment of visual function and retinal imaging

Assessment of visual function and retinal imaging will be performed as outlined in Section 5.6 (Trial Assessments) at baseline and at intervals following intervention. These assessments will be scheduled over a period of a day for visits at day 1, day 3, week 1, week 2, week 4 and week 6 after surgery, and up to 4 days for baseline examinations, and 3 months and 6 months following intervention. For day 1 and 3 refraction cannot reliably be measured. Therefore, the most recent refraction measurement will be used.

All participants (adults and children) will need to be able to perform visual acuity testing and SD-OCT imaging reliably. Other clinical assessments will be undertaken as appropriate for each participant's ability; since there is wide variability in the ability of children of different ages to undertake these tests, the evaluations for children may be restricted to those tests that they are able to perform reliably.

Additional investigations may be performed for appropriate clinical management of any adverse events.

5.4.2.4 Laboratory Procedures

Blood serum will be processed within the UCL Institute of Ophthalmology to assess any immune responses to the ATIMP. Serum will be analysed for:

1. anti-AAV5 antibodies by ELISA
2. anti-human *RPE65* antibodies by ELISA
3. anti-AAV5 neutralising antibodies

Blood serum, saliva and lacrimal fluid will be processed at the UCL Institute of Ophthalmology to assess dissemination of vector after delivery, where the number of rAAV vector genome copies will be measured by polymerase chain reaction (PCR).

Whole blood will be processed at the National Genetics Reference Laboratory in the UK, or a CLIA-accredited molecular diagnostic laboratory in the US, for *RPE65* mutation screening. Standard haematology and biochemistry screen will be carried out at the Trust associated laboratories, or an accredited laboratory in the United States.

5.4.3 Dispensing

5.4.3.1 Receipt and Storage of the Investigational Medicinal Product

The product, which is stable at ≤–50° Celsius, will be stored at < -70° Celsius in secure temperature controlled and monitored -80^0 Celsius freezers at the sponsor's delegated storage facility. Shipping of ATIMP to study sites will be on dry ice, accompanied by a temperature-monitoring device.

On the day of administration of the ATIMP, the prescribed number of vials will be transferred to the operating theatre according to study specific working instructions. The ATIMP will not be refrozen upon thawing prior to the surgical procedure and any remaining product will be discarded according to local procedures.

5.4.4 Dosages

5.4.4.1 Dosages and dosage modifications

Trial participants will receive 1 of 3 different doses of ATIMP within the range proven to be safe in the preclinical animal studies.

1) low dose 1mL at 1.0 x10^{11} vg/mL
2) intermediate dose 1mL at 3.0 x10^{11} vg/mL
3) high dose 1mL at 1.0 x10^{12} vg/mL

The ATIMP has been produced and stored at the concentration of 1.4 x 10^{12} vg/mL. Vector will be diluted immediately prior to intraocular administration in Hartmann's solution at the time of administration for all 3 doses. For participants receiving the low dose of 1.0 x10^{11} vg/mL, the ATIMP will be diluted 14-fold in Hartmann's solution. For participants receiving the intermediate dose of 3.0 x10^{11} vg/mL, the ATIMP will be diluted 4.6-fold in Hartmann's solution. For participants receiving the high dose of 1.0 x10^{12} vg/mL, the ATIMP will be administered diluted 1.4-fold. In each case, up to 1.0 mL ATIMP at the appropriate titre will be administered to the target area. The CI/PI will prepare the appropriate dilution and this will be checked in the operating theatre by a second clinician prior to administration. The check will be recorded in the participant's source data notes.

Further details for dose-escalation criteria are included in Section 4.3.2.

5.4.5 Accountability

The ATIMP will be prescribed for a particular participant by 1 of the Investigators and handled according to the ATIMP Management Plan applicable for each site.

For accurate accountability, the following information will be recorded when the ATIMP is administered:

i. Date
ii. Participant identification number
iii. Batch number
iv. Volume and dose of vector administered
v. Name of Principal Investigator or delegated surgeon administering ATIMP
vi. ATIMP name/code
vii. Trial reference code
viii. Expiry date

Surplus ATIMP will be destroyed according to existing SOPs, using methods suitable for destruction of genetically modified organisms.

A system will be set-up to ensure the traceability of the ATIMP from the starting material, through to administration to the subject and destruction or final disposition. A comprehensive ATIMP management plan and associated SOPs and forms will be in place to ensure that the required accountability and traceability data is collected and retained.

5.4.6 Compliance and Adherence

Full compliance is expected since the ATIMP will be surgically delivered by the CI or a delegated vitreo-retinal surgeon. The aim is to target the administered volume into the subretinal space. Any deviation from this will be noted in the CRF. See section 5.4.8 (Overdose of trial medication) about the assessment of adherence to the protocol defined delivery of the product.

5.4.7 Concomitant Care

Concomitant use of other medications should be avoided unless clinically necessary and should be used with caution, and appropriately documented on study logs where used. All concomitant medications (including steroids) must be recorded in the eCRF from the day of informed consent.

5.4.8 Overdose of Trial Medication

An intraocular administration of ATIMP will be performed by the operating surgeon (CI or a delegated vitreo-retinal surgeon). The volume of vector delivered to the target site will be measured by the syringe plunger and recorded in the CRF.

Any overdose will be reported to the sponsor. This is a Phase I/II exploratory study and the possible impact of any overdose will be considered in the final analysis. Given that this is a single administration study, the trial subject will not be withdrawn but the collected data will be analysed separately in comparison with the data from the participant's baseline assessments and from other treated participants. Any concern about accurate dosing may warrant suspension of the trial pending appropriate investigation.

Overdose of ATIMP may result in development of Adverse Events of various severities that will be recorded and reported as outlined in Section 5.11.3.

5.4.9 Protocol Discontinuation

5.4.9.1 Subject Withdrawal

In consenting to the trial, participants are consenting to ATIMP administration, trial follow-up and data collection.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial participation at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their participation, a reasonable effort should be made to establish this, whilst remaining fully respectful of the participant's rights.

Should a participant withdraw from the study, a withdrawal CRF documenting the reason for withdrawal will be completed, in addition to the procedures and CRF for the final visit (6 month) assessments, with the participant's consent. However, participants will be encouraged to participate in any of the planned schedule for the trial whilst arranging a visit for routine (annual) clinical follow-up.

Participants who withdraw prior to vector administration will be regarded as off-protocol and their primary ophthalmologist will resume normal standard of care. Any subject who withdraws prior to administration of ATIMP may be replaced in the study. Participants who withdraw from the study after vector administration will be encouraged to have follow-up investigations with their consent, so that the consequences of vector administration can be documented and the data analysed. The CMT may choose to replace a subject who withdraws after vector administration.

5.4.9.2 Trial Stopping Rules

The Chief Investigator and Sponsor retain the right to terminate the study. Specific circumstances that may precipitate such termination are as follows:

1. Unanticipated adverse medical experience in this or other studies indicating a potential health hazard caused by the ATIMP
2. Significant protocol deviation and lack of compliance and cooperation on the part of an investigator, which endangers the safety of the participants or the validity of the trial
3. Death of a participant at any time point after ATIMP administration that is possibly, probably, or definitely related to the ATIMP
4. The occurrence of a non-ocular malignancy at any point after gene transfer that is possibly, probably, or definitely related to the ATIMP

5.5 Outcomes

5.5.1 Primary Outcomes

The primary outcome is defined as any of the below occurring during the 9 weeks following administration, at least possibly related to the ATIMP, not surgery alone:

- Reduction in visual acuity by 15 ETDRS letters or more
- Severe unresponsive inflammation

- Infective endophthalmitis)
- Ocular malignancy
- Grade III or above non-ocular SUSAR. (See Section 5.11.3)

5.5.2 Secondary Outcomes

The secondary outcomes are measures of the efficacy of the ATIMP; these will be performed on an individual participant basis and will be descriptive in nature. Secondary outcomes are:

- Any improvements in visual function from baseline that are greater than the test-retest variationand are sustained for at least two consecutive assessments.

- Any improvement in retinal function from pre-intervention that is greater than the test-retest variation and measurable by electroretinography (ERG).

If no ERG is previously detectable, then the presence of any reproducible response with appropriate waveform would be significant. If an ERG is there to start with, any of the following would be significant: an improvement in amplitude of >50 % in DA 0.01 b-wave (rod system sensitivity); bright flash DA 10 a-wave (photoreceptor improvement); the 30Hz flicker; and the LA 3.0 photopic a- and b-waves. In terms of timing: > 3ms improvement in photopic parameters and bright flash DA 10 a-wave; 3-6ms for the DA 0.01 and DA 10.0 b-waves.

- Quality of life will be measured by the Impact of Visual Impairment (IVI) questionnaire and the EQ5D- 5Land EQ-5D-Y

5.6 Trial Assessments

Table 2: Trial assessments

	Screening	Baseline			ATIMP admin	D1	D3	W1	W2	W4	W6	W9	W12	W24
Flexibility of schedule (± days)		- 3 months			Day 0	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 7D	± 14D	± 14D
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Informed consent	•													
Physical exam	•													
Medical history	•							•	•	•	•	•	•	•
Eligibility determination	•													
IMP administration					★									
Adverse event review		•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant medication review	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Genetic screening	•													
Pregnancy test	•				•									
Vital signs (including height and weight)[5]	•	•				•		•	•	•				
Haematology/Renal Function		•				•		•	•	•	•			
Biochemistry/glucose		•				•		•	•	•	•			
Serology		•								•			•	•
PCR						•				•				
QoL questionnaires (IVI and EQ5D-5L)		•												•
Visual acuity[6]	•	•	•	•		•	•	•	•	•	•	•	•	•
Contrast sensitivity	•	•	•	•									•	•
Reading speed		•	•	•									•	•
Colour vision		•	•	•									•	•
Octopus perimetry		•	•	•									•	•
Full field Stimulus Testing[7]		•	•	•									•	•
Microperimetry (mesopic and scotopic)		•	•	•							•		•	•

Visual mobility (PAMELA or Michigan maze)[1]		•[2]												•
Ocular examination	•	•	•	•		•	•	•	•	•	•	•	•	•
Fundus photography		•				•	•	•	•	•	•	•	•	•
Optical coherence tomography	•	•	•	•		•	•	•	•	•	•	•	•	•
Adaptive optics imaging[3]		•	•											•
Fundus autofluorescence		•											•	•
Flash electroretinography[4]	•	•									•		•	•
Pattern electroretinography[4]	•	•									•		•	•
Multifocal electroretinography[4]	•	•									•		•	•

[1] A 6-week window period is permitted around the visual mobility assessments.

[2] Multiple baseline PAMELA assessments may be performed on the same day if considered logistically and clinically appropriate

[3] Adaptive optics imaging baseline assessments may be performed on the same day where considered logistically and clinically appropriate

[4] Additional baseline assessments are permitted if there is inconsistency between the screening and first baseline assessment

[5]Measurements for vital signs include: blood pressure, pulse, respiration rate, arterial oxygen saturation, temperature, height and weight

[6] Visual acuity at day 1 and 3 will be assessed by using the previous refraction.

[7] FST test results will be collected retrospectively (with written consent) for paediatric participants if the assessment has been performed previously

ERG assessments may be performed under general anaesthesia if considered appropriate

5.6.1 Early Stopping of Follow-up

If a participant chooses to withdraw from the trial, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants who stop trial follow-up early may be replaced.

5.6.2 Loss to Follow-up

This is a highly motivated patient group who are likely to remain committed to the research. Continued follow up of all participants will be strongly encouraged whilst being mindful of the importance of ensuring the autonomy of participants in regards to their treatment decisions and willingness to continue to participate in the trial.

5.6.3 Trial Closure

The end of the entire trial is considered the last follow-up visit of the last participant. For each participant, the trial will terminate at the last scheduled visit 6 months following ATIMP administration. The MHRA will be notified of the end of the trial within 90 days of its completion.

5.6.4 Passive/Long Term Follow-Up After the End of the Trial

At the end of this trial, participants will be invited to enrol in a 5-year follow-up study to determine longer term safety and efficacy.

5.7 Sample Size

This is a Phase I/II trial to establish safety and assess indicators of potential efficacy of the ATIMP, therefore there is no formal sample size calculation. The trial will enrol up to 27 participants (up to 18 in the dose escalation phase and a further 9 in the confirmatory phase), as described in section 4.3.2.2. The limited number of participants is necessitated by the rare nature of the disease under investigation. We estimate that inclusion of up to 27 participants will be sufficient to determine the safety and tolerability of the intervention.

5.8 Recruitment and Retention

5.8.1 Recruitment

Most participants will be recruited through Moorfields Eye Hospital or the Kellogg Eye Center, or on referral by ophthalmologists within or outside the UK or the US. Members of their direct clinical care team will approach potential participants in the first instance to discuss whether they would like to consider participating. Alternatively, potential participants may contact the trial team independently.

We expect to recruit up to 27 participants within a period of 36 months.

5.8.2 Retention

Participants will be supported to remain in follow-up by regular contact as per the protocol, provision of a 24-hour hotline to a member of the trial team

5.9 Assignment of Intervention

5.9.1 Allocation

All participants will receive the same intervention in this open label, non-randomised trial: subretinal administration of AAV2/5-OPTIRPE65. The dose received by each participant will depend on the time/order of their enrolment in the trial, and the extent to which dose-limiting events observed in earlier participants during the dose-escalation phase (See Sections 4.3.2 and 5.4.4 for dose escalation information). Children will not be enrolled in the trial until the safety profile and recommended dose have been established in adults.

5.10 Data Collection, Management and Analysis

5.10.1 Data Collection, Management and Entry

Syne qua non will be responsible for data management activities for the study.

Data will be captured in a fully validated, 21 CFR Part 11 compliant Electronic Data Capture (EDC) system provided by Syne qua non.

Syne qua non will grant authorised site staff with access to the EDC system following system training and a successful competency assessment.

Data required by the protocol will first be recorded on source documents (e.g. medical records and study-specific data capture tools as needed) and then entered by site staff into the EDC system. All information in EDC must be traceable to these source documents. Any data recorded directly into EDC will be defined prior to the start of data collection. All data is currently anticipated to be associated with source data records.

Data validation checks will be activated during data entry to identify data discrepancies. Appropriate error messages will be displayed to allow modification or verification of data by the site staff.

Monitoring staff will review the data for completeness and accuracy, instructing site staff to make any required corrections or additions via data queries. Syne qua non will run further automated validation checks and review the data, raising further data queries to the sites for resolution of any inconsistencies.

The Investigator will review the eCRFs for completeness and accuracy then electronically approve the data, retaining full responsibility for its accuracy and authenticity.

Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Prior and concomitant medication will be coded using the World Health Organization Drug (WHO)-Drug Dictionary which employs the Anatomical Therapeutic Chemical (ATC)

classification system. Further coding details and data management processes will be described in a Data Management Plan (DMP).

All actions within the EDC system are captured within an audit trail. After all data have been entered, validated and signed off, the database will be locked.

At the end of the study, PDF copies of the eCRFs for each subject and supporting information will be provided to sites and the Sponsor. The electronic data will be provided to the Sponsor.

5.10.3 Non-Adherence and Non-Retention

Participants who withdraw from the trial after the intervention will be encouraged to participate in any of the planned follow-up scheduled for the trial with their consent, and data from these subjects collected prior to withdrawal may be included in the interpretation of results.

Reasons for withdrawal from the trial will be documented on a withdrawal CRF where possible, in addition to the procedures and CRF for the final visit (6 month) assessments with the participant's consent.

5.10.4 Statistical Methods

5.10.4.1 Statistical Analysis Plan

A formal statistical analysis plan will be written by the trial sponsor and approved by the IDMC. This trial is an open label, no crossover, Phase I/II trial involving a small number of participants, and analysis of the primary and secondary outcomes will be descriptive in nature.

5.10.4.2 Statistical Methods – Primary Outcome Analysis

The primary outcome is safety of subretinal administration of the ATIMP, defined as any of the below occurring during the 9 weeks following administration, at least possibly related to the ATIMP, not surgery alone:

- Reduction in visual acuity by 15 ETDRS letters or more
- Severe unresponsive inflammation
- Infective endophthalmitis
- Ocular malignancy
- Grade III or above non-ocular SUSAR (See Section 5.11).

The number of DLEs at each dose level will be summarised by cohort and overall.

It is anticipated that the vector will be administered at the MTD in up to 15 participants (6 adults in the dose escalation phase and up to 9 further adults and children in the confirmatory safety phase). Safety data relating to these participants will allow estimation of an upper bound for the true event rate through a 95% confidence interval.

5.10.4.3 Statistical Methods - Secondary Outcome Analysis

The secondary outcomes are measures of the efficacy of the ATIMP; these will be performed on an individual participant basis and will be primarily descriptive in nature. Standard assessments will be used to measure visual function and established methods of analysis, appropriate for the assessment will be used to evaluate the data. For specialist assessments, data will be analysed by the expert team member(s) who developed the assessment. Final data will be reported descriptively.

Efficacy will be indicated by:

1) Any improvement in visual function from baseline that is greater that the test-retest variation for that test and is sustained for at least two consecutive assessments.

2) Any improvement in retinal function from pre-intervention assessment that is greater than the test-retest variation and measurable by electroretinography (ERG)

If no ERG was previously detectable, then the presence of any reproducible response with appropriate waveform would be clinically significant. If an ERG was there to start with, any of the following would be significant:

- an improvement in amplitude of >50 % in DA 0.01 b-wave (rod system sensitivity);
- bright flash DA 10 a- wave (photoreceptor improvement);
- the 30Hz flicker; and
- the LA 3.0 photopic a- and b-waves.

In terms of timing: > 3ms improvement in photopic parameters and bright flash DA 10 a-wave; 6ms for the DA 0.01 and DA 10.0 b-waves.

Measures will be reported individually and aggregated across participants as the proportion who satisfy the above criteria.

Quality of life patient reported outcome measures will be used to correlate a participant's feeling about their own wellbeing with clinical observations.

Any deviations from the original statistical plan will be approved by the CMT and IDMC and described in the final report, as appropriate.

5.10.4.4 Statistical Methods – Health Economic Analysis

No health economic evaluation is planned, but the collection of EQ5D would allow QALYs to be calculated.

5.11 Data Monitoring

5.11.1 Independent Data Monitoring Committee (IDMC)

To ensure the safety and efficacy and overall trial conduct, an IDMC will be established and take part in the data monitoring. The IDMC will consist of members with specific expertise in ophthalmology and molecular genetics. The IDMC will make recommendations on the safety data prior to any dose change, and prior to the first participant aged under 16 being included in the trial.

Further details of the roles and responsibilities of the IDMC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the Gene Therapy Trial for LCA OPTIRPE65 IDMC charter.

5.11.2 Interim Analyses

No formal interim analysis is planned within the trial, but periodic reports concerning participant safety and key efficacy outcomes will be prepared for the IDMC as agreed in the Terms of Reference.

5.11.3 Data Monitoring for Harm

5.11.3.1 Safety reporting

EMAS Pharma will be responsible for pharmacovigilance services.

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 3: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***

SUSAR	Suspected Unexpected Serious Adverse Reaction

*the term life threatening here refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent 1 of the other outcomes listed in the table (e.g. a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

Adverse events include:

- an exacerbation of a pre-existing illness
- an increase in the frequency or intensity of a pre-existing episodic event or condition
- a condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after trial drug administration)
- continuous persistent disease or a symptom present at baseline that worsens following ATIMP administration

Adverse events do NOT include:

- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before ATIMP administration that does not worsen
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms

5.11.3.2 Other Notifiable Adverse Events

In order to manage the safety risks associated with administration of the vector, all safety events will be reviewed within a short time frame for all participants, as described in the OPTIRPE65 Data Management Plan. Pregnancy is the only additional notifiable event that requires expedited reporting.

5.11.3.3 Procedures to follow in the event of female participants becoming pregnant

A pregnancy test will be conducted for all females of child bearing age and the results will be recorded in the medical notes before enrolling a volunteer to the trial. Females with a positive pregnancy test at this point will be excluded from the trial.

A further pregnancy test will be performed on the day of administration of the ATIMP. Female participants with a positive pregnancy test at this point will be excluded from the trial prior to administration of the ATIMP.

Although participants are instructed to use double barrier contraception, we cannot exclude entirely that a participant might become pregnant after administration of the ATIMP. In the unlikely event that a participant is found to be pregnant we will notify their GP that she is participating in a gene therapy trial and that, although the risks involved are minimal, there is a chance of gene transfer to the unborn child. With the participant's consent, we will ask the GP/obstetrician to provide us with regular reports about the pregnancy until delivery. The pregnancy will be reported to EMAS Pharma within 24 hours of the investigator becoming aware of the event. We will continue follow-up of the participant until outcome of the pregnancy. However, if the participant is unable or unwilling to participate further in the trial, she will be encouraged to continue clinical monitoring visits to assess ocular health. In that situation, we may choose to enrol another participant to ensure the scientific validity of the trial.

5.11.3.4 Procedures to follow in the event of the partners of male participants becoming pregnant

Although participants are instructed to use double barrier contraception, we cannot exclude entirely that the partner of a participant might become pregnant after administration of the ATIMP. In the unlikely event that this occurs we will notify the participant's GP that he is participating in a gene therapy trial and that, although the risks involved are minimal, there is a chance of gene transfer to the unborn child. With the participant's consent, we will contact the partner to ascertain the status of the pregnancy and the outcome. The pregnancy will be reported to EMAS Pharma

5.11.3.5 Investigator responsibilities relating to safety reporting

The Investigator will assume overall responsibility for evaluating and reporting adverse events. In urgent situations a member of the trial team may report on their behalf, while making every effort to discuss the event with them. All non-serious AEs and ARs including all events observed following ATIMP administration, whether expected or not, should be recorded in the participant's medical notes and in the eCRF. These should be entered on to the database according to the timelines defined in the Gene Therapy for LCA OPTIRPE65 Data Management Plan to allow appropriate monitoring by the CMT. SAEs and SARs should be notified to EMAS Pharma within 24 hours of the investigator becoming aware of the event.

Clinically significant abnormalities in the results of objective tests will also be recorded as adverse events. If the results are not expected as part of disease or surgery these will also be recorded as unexpected. There are currently no expected events associated with the ATIMP.

All serious adverse events will be recorded in the hospital notes and the CRF. Adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All adverse events will be recorded until the end of the trial (refer to Section 5.6.3 for definition), or until pregnancy outcome in the case of pregnancy. All SAEs will be recorded, fully investigated and appropriately managed until resolution or stabilisation and CI sign off.

5.11.3.5.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table3. If the event is classified as 'serious' an SAE form must be completed and emailed to EMAS Pharma, notified within 24-hours of the investigator becoming aware of the event.

5.11.3.5.2 Severity or grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity grading in NIH CTCAE Version 4.0 (NIH, 2009).

Table 4: Grading of Adverse Events

Category	Definition
Mild (Grade I)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade II)	Minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL*
Severe (Grade III)	Severe or medically significant but not immediately life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**
Grade IV	Life threatening consequences; urgent intervention indicated
Grade V	Death related to AE

* Instrumental ADL (Activities of Daily Living) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

5.11.3.5.3 Causality

Causality will be assessed in terms of both the ATIMP and the surgical procedures. Based on all available information at the time of completion of the case report form, the investigator must assess the causality of all serious events or reactions. It is of particular importance in this trial to capture and differentiate events related to:

- The ATIMP administration surgery
- The ATIMP

The differentiated causality assessments will be captured in the trial specific CRF and SAE form using the definitions in Table 5.

Table 5: Causality definitions

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

5.11.3.5.4 Expectedness

In view of the very limited clinical experience with the ATIMP there are at present no events considered as expected for the ATIMP. Therefore, any SAEs that are related to the ATIMP (i.e., considered a SAR) will be deemed a SUSAR (suspected, unexpected, serious adverse reaction) and MHRA, REC/IBC, FDA, and NIH reporting guidelines apply (see Notifications sections of the protocol).

Table 6: Assessment of expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information about the surgery listed in the Investigator Brochure or clearly defined in the protocol. In view of the very limited clinical experience with the ATIMP there are at present no events considered as expected for the ATIMP listed in the current Investigator Brochure.
Unexpected	An adverse event that is classed in nature as serious and which is not consistent with the information about the ATIMP and surgery listed in the Investigator Brochure*or clearly defined in the protocol.

*This includes listed events that are more frequently reported or more severe than previously reported

The reference document to be used to assess expectedness against the ATIMP and surgery is the Investigator Brochure. Procedure-related adverse events cannot be considered expected to the ATIMP. Previous experience with AAV-mediated gene therapy in the retina indicates that the risks are largely limited to the eye. A temporary and/or mild decrease in visual acuity, due to detachment of the retina or post-surgical inflammation, is to be expected after intraocular surgery and will not cause undue discomfort to the participants. Therefore, we have defined the success criteria for the primary outcome (safety) as the absence of an adverse event that has a substantial and sustained negative impact on vision, as well as the absence of any non-ocular SUSAR.

Expected events associated with surgery:

- Temporary and/or mild decrease in visual acuity, due to detachment of the retina or post-surgical inflammation
- Ocular discomfort
- Epiphora
- Periocular swelling
- Diplopia
- Ptosis
- Subconjunctival or intraocular haemorrhage
- Corneal abrasion
- Retinal tear or detachment
- Wound leak
- Ocular hypotony or raised intraocular pressure
- Overfill or underfill of any intraocular gas tamponade
- Mild intra- or extra-ocular inflammation
- Scleral or conjunctival suture granuloma
- Lens opacity or dislocation
- Systemic adverse events related to sedation or general anaesthesia, including nerve or vascular injury

5.11.3.6 Notifications

5.11.3.6.1 Notifications by the Investigator to EMAS

All adverse events will be recorded in the hospital notes and the CRF from the date of written informed consent until last study visit. Investigators should notify EMAS of any SAEs occurs during this period. After last visit, any SAE reported to the investigator and considered causally related to trial treatment should be reported as part of the follow up study. For any participants that do not go into the follow up study, then SAEs that occur after the end of the trial and that may be attributed to ATIMP administration should be reported to the relevant regulatory agencies.

EMAS must be notified of all SAEs and SUSARs within 24 hours of the investigator becoming aware of the event. The investigator will respond to any SAE queries raised by the sponsor as soon as possible.

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to EMAS. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the trial team on drug.safety@emaspharma.com

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of trial follow-up (i.e. 6 months after delivery of ATIMP) if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to EMAS as further information becomes available. Additional information and/or copies of test results may be provided separately. The participant must be identified by trial number and date of birth only. The participant's name should not be used on any correspondence and must be blacked out and replaced with trial identifiers on any test results if the name is shown.

5.11.3.6.2 Reporting Urgent Safety Measures

The sponsor or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.

If any urgent safety measures are taken, MeiraGTx UK II Ltd. shall immediately (no later than 3 days from the date the measures are taken), give written notice to the MHRA, the relevant REC and the Sponsor of the measures taken and the circumstances giving rise to those measures.

5.11.3.6.3 EMAS responsibilities

EMAS will follow EMAS Standard Operating Procedures and a study specific Safety Management Plan to ensure that case processing of events occurs within appropriate regulatory timeframes. EMAS will submit Development Safety Update Reports (DSURs) to regulatory authorities.

5.11.3.6.4 Reporting SUSARs in International Trials

The mechanism for reporting SUSARs that occur outside of the UK to the MHRA, and those that occur outside of the US to the FDA will be covered in the trial specific Safety Management Plan.

5.11.3.6.5 Annual Progress Reports

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. Annual IRB applications for continuing review will be submitted with sufficient time to allow review and approval of trial continuation.

5.11.4 Quality Assurance and Control

5.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the Gene Therapy for LCA OPTIRPE65 trial are based on the MeiraGTx UK II Ltd. Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

5.11.4.2 Clinical Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the trial Monitoring Plan (MP). The MP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority MeiraGTx UK II Ltd. must be notified as soon as possible.

5.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC/IRB review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this will be obtained as part of the informed consent process for the trial.

5.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the Monitoring Plan.

5.11.4.4.1 Clinical Management Team

A Clinical Management Team (CMT) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the CMT terms of reference.

5.11.4.4.2 Independent Data Monitoring Committee

The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the CMT on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the CMT through its Chair.

5.11.4.4.3 Trial Sponsor

The role of the sponsor is to undertake regulatory responsibilities, and to secure arrangements to initiate, manage and finance the trial. MeiraGTx UK II Ltd. is the trial sponsor.

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC/IRB for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local approval. An annual progress report or application for annual Continuing Review will be submitted to the relevant REC/IRB at each clinical trial site.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant, has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if the clinician feels it to be in the best interest of the participant. The reasons for doing so must be recorded. The participant remains free to change their mind at any time about the ATIMP administration (before administration) and follow-up (at any time) without giving a reason and without prejudicing their further treatment.

6.2 Competent Authority Approvals

This protocol will be submitted to the national competent or equivalent authority (i.e. MHRA in the UK and Food and Drug Administration (FDA) in the US).

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

This is a Clinical Trial of an Investigational New Drug as defined by 21CFR Part 312 of the Code of Federal Regulations. Therefore, an Investigational New Drug Application (IND) is required in the US.

This trial is a human gene transfer study and therefore in the US must be reviewed by the initial site's Institutional Biosafety Committee and possibly by the Recombinant DNA Advisory Committee (RAC) of the NIH's Office of Biotechnology Activities (OBA).

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the Competent Authority, regulatory agency or equivalent in accordance with relevant national and local requirements and practices.

6.3 Other Approvals

The protocol will be submitted by those delegated to do so to the local department of each participating site. A copy of the local approval (or other relevant approval as above) and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to MeiraGTx UK II Ltd. as part of the site initiation process prior to the site being designated 'open to recruitment' status.

Participating sites receiving funding or support from the US government will obtain a Federal Wide Assurance (FWA). For ATIMP trials using Genetically Modified Organisms, organisations should also receive approval from their relevant national body to use the product (i.e. notification to the HSE in the UK).

6.4 Protocol Amendments

MeiraGTx UK II Ltd. will be responsible for amendments to the protocol. MeiraGTx UK II Ltd. will be responsible for ensuring that protocol amendments are submitted to national competent authorities, and to investigators at each clinical trial site.

Investigators at each clinical site will be responsible for submitting protocol amendments to the relevant REC/IRBs for approval, as well as any additional competent authorities in each country that require notification (e.g. the NIH OBA).

6.5 Consent or Assent

Potential participants will be provided with a Participant Information Sheet (PIS) and given time to read it fully. Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant (or parent or guardian of a child) is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment (or that of their child).

Minors who are unable to consent for themselves will not be enrolled in the trial without the consent of their parent(s) or legal guardian(s). Children or adolescents will be asked to assent or agree. A Participant Information and Assent sheet that describes the details of the trial, trial procedures, and risks in simplified form will be provided to minors who have the capacity to provide informed assent. Participation must be refused in the event that assent is not given. Assent forms do not substitute for the consent form signed by the participant's legally authorized representative.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the participant information sheet and the participant will be asked to sign an updated consent form. These will be approved by the appropriate ethics committee prior to their use. Consent will also be re-sought in the event that a child's carer changes.

A copy of the approved consent form is available from MeiraGTx UK II Ltd.

6.6 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998 and 2018 or the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

These regulations require a signed subject authorization informing the participants of the following:

- What protected health information (PHI) will be collected from participants in this trial
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled trial period.

Participant confidentiality will be held strictly in trust by the investigators, trial staff, and the sponsor and their agents, to the extent provided by Federal, state, and local law. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any trial information relating to participants. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will use coded numbers only. Participants will not be identified in any publicly released reports of this trial.

Access to trial records will be limited to the minimum number of individuals necessary for quality control, audit and analysis. Clinical information will not be released without written permission of the subject, except as necessary for trial-related monitoring, audits, REC/IRB review, and regulatory inspections by University or government entities. In such cases, the clinical trial site will provide direct access to all source data, documents, and records maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the trial participants. Trial participants will be informed of this during the informed consent process.

No information concerning the trial or the data will be released to any unauthorized third party without prior written approval of the MeiraGTx UK II Ltd.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The date of birth and participant identification number, will be used for identification.

6.7 Declaration of Interests

The trial is funded by MeiraGTx UK II Ltd.

James Bainbridge declares a financial interest in the company and receipt of payment for consultancy services.

Michel Michaelides declares a financial interest in the company and receipt of payment for consultancy services.

6.8 Indemnity

MeiraGTx UK II Ltd. holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that MeiraGTx UK II Ltd. has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. MeiraGTx UK II Ltd. does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of MeiraGTx UK II Ltd. or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to MeiraGTx UK II Ltd.'s insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to MeiraGTx UK II Ltd., upon request.

6.9 Finance

The Gene Therapy Trial for LCA OPTIRPE65 is funded by Medical Research Council grant number MR/M015815/1 and by MeiraGTx UKII Ltd. It is not expected that any further funding will be sought.

6.10 Archiving

6.10.1 Archiving of Essential Trial Documentation Relating to Traceability

Requirements for a traceability system and document archiving will be met in line with Regulation 1394/2007 on Advanced Therapy Medicinal Products and the applicable Directives therein. To comply with the regulatory requirements, each responsible party (the sponsor of the trial, the manufacturer and the investigator(s)/institution(s) where the ATIMP is used) will ensure that the information relating to the traceability and accountability, from the production of ATIMPs to the recipient (participant)

receiving the ATIMPs, are archived for a minimum of 30 years after the expiry date of the ATIMP. These requirements will be set out in contractual agreements between the parties and the sponsor.

The following essential documents/traceability data will be retained by the investigator and institution responsible for the human application of the ATIMP:

- Shipping Records for the ATIMP
- Certificate of Analysis of the ATIMP
- Subject identification code list
- ATIMP accountability at the site including final disposition of both used and unused product

These records contain relevant information for traceability purposes and at least the following minimum data set from these records should be kept for 30 years after the expiry date of the product, or longer if required by the terms of the clinical trial authorisation or by the agreement with the sponsor:

- Identification of the investigator/institution
- Identification of the sponsor
- Identification of the manufacturing site
- Product name/code
- Pharmaceutical form, route of administration, quantity of dosage units and strength
- Batch number
- Trial reference code
- Trial Participant code
- Participant identification code list (links name of recipient to the trial participant code)
- Product expiry/retest date
- Date of administration
- Participant medical record should also contain the product name/code, the trial reference code, trial participant code and administration dates and doses
- Records of any product that was unused or destroyed at site and its final status

6.10.2 Archiving of Other Essential Trial Documentation

Trial documents should be retained for a minimum of 2 years after an FDA marketing application is approved for the ATIMP and until there are no pending or contemplated marketing applications for the ATIMP, or if an application is not approved for the ATIMP, until 2 years after shipment and delivery of the drug for investigational use has been discontinued and FDA is notified. For gene therapy trials, current Federal and State of Michigan requirements state that research records should be kept indefinitely, until further notice. Archiving of REC/IRB notices should be maintained according to local and/or institutional requirements.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

MeiraGTx UK II Ltd. will notify sites when trial documentation can be archived, and which documents must be archived for the 30-year period. All archived documents must continue to be available for inspection by appropriate authorities upon request.

Destruction of essential documents will require authorisation from the Sponsor.

6.11 Access to Data

The investigators/ institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections, providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the CMT. Considerations for approving access are documented in the CMT Terms of Reference.

6.12 Ancillary and Post-Trial Care

Participants will be invited to participate in a follow-up study after completion of this trial.

6.13 Publication Policy

6.13.1 Trial Results

All proposed scientific publications will be discussed with the Sponsor prior to publication. Since this is an exploratory, open-label, Phase I/II trial, progress and significant findings may be presented at scientific forums/meetings and/or published during the course of the trial.

The results of the trial will be disseminated regardless of the direction of effect.

7 Ancillary Studies

There are no currently planned ancillary studies. Any future ancillary studies will be subject to separate funding, and will be submitted for ethical and regulatory review as appropriate.

8 Revision History

Protocol Version and Date	**Reason for Amendment**
Protocol V1.1 dated 28.01.2016	Clarify safety reporting procedures as requested by MHRA
Protocol V2 dated 6th June 2016	Further clarification of safety reporting procedures as requested by the MHRA. Updated inclusion/exclusion criteria as requested by the US FDA. Enhanced description of the method of measuring the primary objective and outcome Enhanced description of the dose limiting criteria

	Minor modification to wording and language to correct typographical errors and ensure consistency throughout Change in name of funder from Athena Vision Ltd. to MeiraGTx UK Ltd.
Protocol V3 dated 2nd August 2016	Visual acuity assessments at day 1 and day 3 post-treatment had been erroneously omitted from V2. These were replaced. UCL CCTU Clinical Project Manager was replaced and details updated.
Protocol V4 dated 10 February 2017	To reflect the change in sponsor from UCL to MeiraGTx UK II Ltd. Minor modification to wording and language to correct typographical errors and ensure consistency throughout To clarify the DLE and safety definitions To clarify the primary objective and outcome measures To describe the outsourcing of data management, pharmacovigilance and clinical monitoring to CROs
Protocol V5 dated 12 April 2017	To extend the course of post-surgery prophylactic steroids from 4 weeks to 8 weeks. Consequently, the duration for considering dose limiting events has been extended from 6 weeks to 9 weeks to cover the period of steroid administration and one additional week and other minor clarifications
Protocol V6 dated 21 August 2017	To update the prophylactic steroid regimen in children, and clarify safety reporting and safety dose for children
Protocol V7 dated 23 February 2018	To clarify the allowance of data obtained from the natural history study be used for screening and or baseline assessments (with consent from subjects) in order to avoid unnecessary testing of subjects. Clarify that more than 1 surgeon at a site may inject vector

	Expand the number of categories for ATIMP administration surgery from related or unrelated to: unrelated, unlikely, possibly, probably or definitely
Protocol V8 dated 11 June 2018	To add Full field Stimulus Testing as an assessment for children

9 References

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