MEIRAGTx

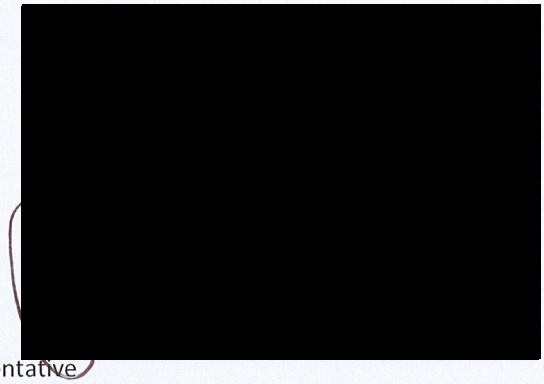
Gene Therapy for Achromatopsia (*CNGB3*)

An open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV2/8-hCARp.hCNGB3) for gene therapy of adults and children with achromatopsia owing to defects in *CNGB3*

Version	Version 7.0
Date	29 Jan 2019
Sponsor	MeiraGTx UK II Ltd.
Sponsor's Protocol Number	MGT006
Trial registration	EudraCT 2016-002290-35
CTA #	45522/0001/001-0001
NRES #	16/LO/1540

Authorisation: Chief Investigator

Name
Role



Signature

Date

Authorisation: Sponsor Representative

Name
Role
Signature

Date

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1 Administrative information

This document describes the Gene Therapy for Achromatopsia (*CNGB3*) 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 the treatment of 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. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at MeiraGTx UK II Ltd.

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 the 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, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2006/1928 and subsequent amendments, Advanced Therapy Medicinal Products (ATMP) Regulations (EC) No 1394/2007, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the General Data Protection Regulation 2016/679, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). US sites will comply with 21 CFR 312 in the Code of Federal Regulations, and the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (November 2013).

The participating sites will inform MeiraGTx UK II Ltd. as soon as they are aware of a possible serious breach of compliance, so that MeiraGTx UK II Ltd. can fulfil its requirement to report the breach if necessary, 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	EudraCT 2016-002290-35
Secondary Identifying Numbers	MeiraGTx UK II Ltd. registration number: MGT006
Source of Monetary or Material Support	MeiraGTx UK II Ltd.
Sponsor	MeiraGTx UK II Ltd.
Contact for Public Queries	ocularinfo@meiragtx.com
Contact for Scientific Queries	[redacted]
Public Title	Gene Therapy for Achromatopsia (*CNGB3*)
Scientific Title	An open label, multi-centre, Phase I/II dose escalation trial of an adeno-associated virus vector (AAV2/8-hCARp.hCNGB3) for gene therapy of adults and children with achromatopsia owing to defects in *CNGB3*
Countries of Recruitment	United Kingdom, United States of America
Health Condition	Achromatopsia
Intervention(s)	Open label, non-randomised, dose-escalation ([redacted], Phase I/II study, by subretinal administration of AAV2/8-hCARp.hCNGB3 in up to 36 participants with achromatopsia owing to mutations in the *CNGB3* gene.
Key Inclusion and Exclusion Criteria	Key Inclusion Criteria: • Aged 3 years or older (children will be included only once the maximal tolerated dose has been determined) • Achromatopsia caused by mutations in *CNGB3* • Evidence of preservation of photoreceptors at the macula • 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 • Intra-ocular surgery within 6 months of screening

	• Ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results. • Participated in another research study involving an investigational therapy for ocular disease within the last 6 months • Have any other condition that the PI considers makes them inappropriate for entry into the trial • Are unwilling to consider the possibility of entry into a subsequent longer term follow up study
Study Type	Phase I/II, open-label, non-randomised, 2 centre, dose escalation in adults, followed by dose confirmation in adults and children with achromatopsia owing to defects in *CNGB3*
Date of First Enrolment	Anticipated Q4 2016
Target Sample Size	Up to 36 participants
Primary Outcome(s)	The primary outcome is safety of subretinal administration of AAV2/8-hCARp.hCNGB3. 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 in this study, and a further 4.5 years in a separate subsequent study.
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. Efficacy will be assessed at several time points between 3 to 6 months after the intervention: 1) Any improvement in visual function from baseline that is greater than 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

Agreements that include detailed roles and responsibilities will be in place between participating sites and MeiraGTx UK II Ltd.

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

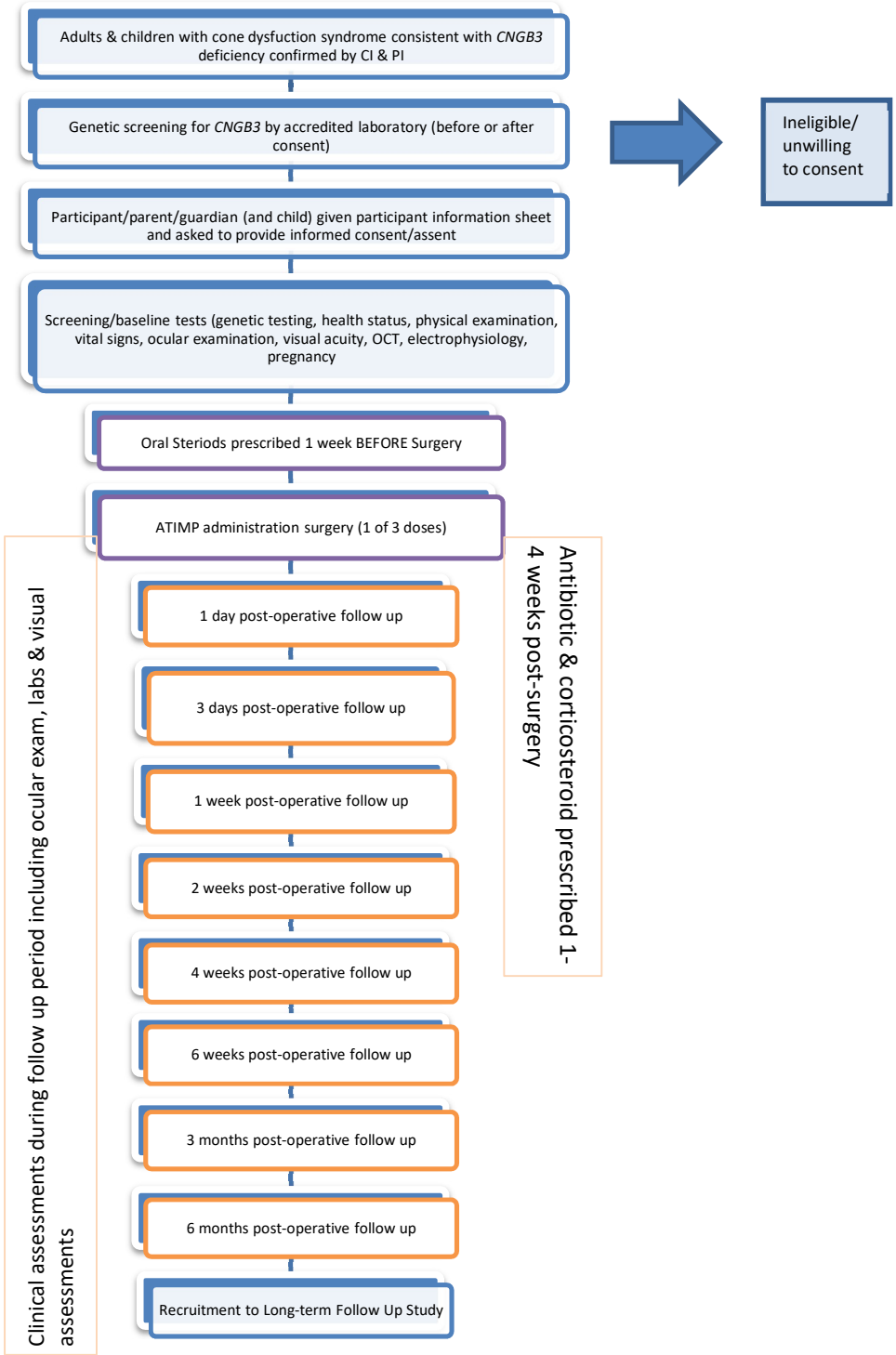
1.4.1 Protocol contributors

Name	Affiliation	Role and responsibilities
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1.4.2 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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
ATMP	Advanced Therapy Medicinal Products
Bd	*Bis die* twice daily
BIOM	Binocular Indirect Ophthalmo Microscope
CA	Competent Authority
cDNA	complementary Deoxyribonucleic Acid
CEO	Chief Executive Officer
cGMP	cyclic guanosine monophosphate
CI	Chief Investigator
CMT	Clinical Management Team
CNGB3	Cyclic Nucleotide-Gated cation channel Beta-3
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DLE	Dose-limiting event
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
ELISA	Enzyme-linked Immunosorbent Assay
ELISPOT	Enzyme-linked ImmunoSpot Assay
EMA	European Medicines Agency
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
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GMSC	Genetic Modification Safety Committee
GTAC	Gene Therapy Advisory Committee
hCAR	Human Cone Arrestin
HIPAA	Health Insurance Portability and Accountability Act
HRA	Health Research Authority
HSE	Health and Safety Executive
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
ISCEV	International Society for Clinical Electrophysiology of Vision
[redacted]	[redacted]
LCA	Leber congenital amaurosis
mfERG	Multifocal Electroretinography

MHRA	Medicines and Healthcare products Regulatory Agency
mL	Millilitre
ms	Millisecond
mRNA	Messenger RNA
MTD	Maximum Tolerated Dose
NHS	National Health Service
NIH	National Institutes of Health
NIMP	Non-Investigational Medicinal Product
OBA	Office of Biotechnology Activities
OCT	Optical Coherence Tomography
PCR	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 daily)
QOL	Quality of Life
QP	Qualified Person for release of ATIMP
rAAV	Recombinant adeno associated virus

REC	Research Ethics Committee
RG	Research grade
RGF	Research Governance Framework
RNA	Ribonucleic acid
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD-OCT	Spectral Domain Optical Coherence Tomography
SOP	Standard Operating Procedure
SSA	Site Specific Approval
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV40	Simian virus 40
TMF	Trial Master File
tRNA	Transfer ribonucleic acid
UAR	Unexpected Adverse Reaction
[redacted]	[redacted]
UK	United Kingdom of Great Britain & Northern Ireland
USA	United States of America
vg	Viral Genomes
[redacted]	[redacted]
WT	Wild type

4 Introduction

4.1 Background and Rationale

4.1.1 Background

Achromatopsia is a recessively inherited condition characterised by a lack of cone photoreceptor function resulting in impairment of colour vision and visual acuity, central scotoma often with eccentric fixation, disabling hypersensitivity to light (photophobia) and involuntary eye movements (nystagmus), (Kohl *et Al.,* 2013; Aboshiha *et Al.,* 2015; Michaelides *et* Al., 2004). In the United States, Achromatopsia is estimated to affect 9,566 individuals (Judd, 1943; Sharpe *et* Al., 1990; Sharpe *et* Al., 1999), in 50% of whom (4,783) the condition results from mutations in the *CNGB3* gene (Kohl *et Al.*, 2005).

Achromatopsia resulting from mutations in *CNGB3* has several characteristics that make it a good candidate disease to demonstrate proof-of-principle in a first-in-man trial of gene therapy for photoreceptor disease. Effective improvement in cone photoreceptor function, which is otherwise absent (or markedly reduced) in this condition, would provide a clear, rapid and reliable measure of outcome. In addition, achromatopsia is largely non-progressive and the extended survival of cones, despite their profound lack of function, presents a wide window of opportunity during which gene supplementation could lead to significant benefit in cone-mediated vision. Although younger individuals may benefit most from gene supplementation therapy by virtue of their greater visual plasticity, we anticipate that the intervention may offer benefit across a range of ages and we aim to define this range. For this reason, participants of various ages will be included; children (as defined by age in section 4.3) will be included once an acceptable safety profile has been established in adults.

4.1.2 Pre-clinical data

In preclinical studies using a murine model of *CNGB3*-deficiency, we have demonstrated that delivery of a functional copy of the h*CNGB3* cDNA sequence to cone photoreceptors is associated with substantial improvements in cone function and morphology (Carvalho, *et al* 2011). Subretinal injection of AAV2/8-hCARp.hCNGB3 of (2.0 x 10^{12} vg/mL) restores CNGB3 protein in cone outer segments, prolongs cone survival, and substantially improves photopic ERG amplitudes (cone-mediated responses on electroretinography) in mice ranging in age from 15 days to 6 months. In younger animals improved cone function results in a complete recovery of cone-mediated vision as assessed by optomoter responses. These findings in mice demonstrate one of the most effective rescues of an animal model of a photoreceptor defect reported to date, suggesting that achromatopsia in humans may also benefit from gene supplementation therapy. These results are supported by a study by Komaromy and coworkers, demonstrating successful gene supplementation therapy in a dog model of the same condition (Komaromy, *et al* 2010).

4.1.3 Clinical data

This protocol describes our group's 3rd clinical trial of a gene supplementation therapy for inherited retinal disease using a recombinant AAV (rAAV) vector. In the first gene therapy trial (Bainbridge, *et al* 2008) 12 participants with severe early onset retinal dystrophy caused by mutations in the gene encoding RPE65 were administered rAAV vector subretinally. Vector administration was generally well tolerated and 6 of the 12 participants benefitted with improved visual function to varying

extents during the first year. However, longer-term follow-up demonstrated that progressive degeneration continued and maximal improvements in retinal sensitivity were not maintained (Bainbridge, *et al* 2015). Similar observations have been described in other independent trials where rAAV2/2 vectors were administered for the same condition by sub retinal administration (Maguire, *et al* 2008; Cideciyan, *et al* 2008; Cideciyan, *et al* 2013). In these studies, subretinal administration of rAAV vectors resulted in visual improvement without significant safety concerns. We are currently investigating the safety and potential efficacy of a new optimized rAAV2/5 vector for delivery of *RPE65* in a trial with a similar design and protocol to this proposed trial [redacted] in up to 27 adults and children with retinal dystrophy caused by mutations in *RPE65*.

4.1.4 Rationale

We predict that in *CNGB3*-related Achromatopsia, delivery of a cDNA sequence encoding a functional CNGB3 protein using gene supplementation will lead to measurable improvements in visual function within 6 months.

There is currently no effective treatment available for most hereditary retinal disorders including achromatopsia. This condition is characterised by absent (or markedly reduced) cone function resulting in profound reduction in visual acuity, complete lack of (or markedly reduced) colour vision, marked photophobia and nystagmus. The *CNGB3* gene encodes the beta subunit of the cone photoreceptor-specific cGMP-gated cation channel, which is critical for cellular responses to light. Absence of this beta subunit results in absent/extremely poor cone function and hence very poor daylight vision. Although loss of cone photoreceptor cells may occur in a limited number of patients, the rate of cell death is very slow, resulting in retinas containing surviving but non-functioning cones. Improvement of cone function by provision of *CNGB3* could provide a clear, rapid and reliable measure of outcome. Furthermore, the relatively non-progressive nature of Achromatopsia, with extended survival of cone photoreceptors, means that the window of opportunity for effective intervention by gene supplementation may extend into adulthood.

However, since achromatopsia results in marked visual impairment from birth, associated abnormal development of physiological cone-dependent neuronal circuits, including that of the visual cortex, may limit the potential for older individuals to benefit from therapeutic restoration of retinal function. Since visual cortical plasticity is known to be greater in younger children, we will recruit children once an acceptable safety profile has been defined in adults. Older participants might benefit with relief from photophobia even if limited cortical plasticity affects the potential for improved acuity or colour vision.

4.1.5 Assessment and management of risk

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. *CNGB3*-related Achromatopsia results in profound sight impairment from birth or early infancy. The condition is currently untreatable, but there is a real possibility that gene therapy could offer a significant benefit in terms of improved sight and quality of life (QOL), based on our own experience from the first clinical trial for ocular gene therapy, subsequent ocular gene therapy trials elsewhere (Maguire, *et al* 2008; Cideciyan, AV *et al* 2008 and 2013), and pre-clinical data demonstrating improved outcome in *CNGB3*-related achromatopsia. Possible benefits of improved

cone-photoreceptor function include, improved visual acuity, improved colour perception, and relief from disabling photophobia.

The safety of the proposed approach will be enhanced by restricting transgene expression to the target tissue by virtue of rAAV vector tropism and the cone-specific promoter sequence used, and by restricting the intervention to one eye only in each participant. The risk of adverse effects will be further minimised by minimising the volume of vector suspension administered and by targeting it surgically to the cone rich region of the central retina.

Risks to participant safety in relation to the ATIMP is classified using the MHRA definition as Type C (Markedly higher than the risk of standard medical care). General risk management includes the detailed review of all 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 longer-term risks. Details of specific risks and their management strategies are outlined below.

4.1.5.1 Risk of immune responses to AAV2/8-hCAR.hCNGB3

The main risk of inflammation will be 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 treatment using topical and systemic corticosteroids. . Persistent intraocular inflammation will be managed by topical corticosteroid therapy, with systemic corticosteroids where indicated.

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 our subsequent trial of gene therapy, intraocular administration of an AAV2/5 has been well tolerated in 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 AAV, anterograde and trans-synaptic transport of small amounts of vector genome from the retina to central visual structures may occur (Stieger, *et al* 2008). This is considered most likely to result from off target transduction of retinal ganglion cells following reflux of vector suspension into the vitreous. Since only tiny amounts of vector are likely to reach the brain and a cone photoreceptor-specific promoter will be used, the possibility of transgene expression causing toxicity in the brain is considered to be highly unlikely. Minimal vector amounts (i.e. a few hundred vector genome copies) might be traced in other organs like lymph nodes, spleen and liver but similarly to the brain; transgene expression causing toxicity is highly unlikely due to the cone photoreceptor-specific promoter.

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) AAV vector genomes integrate into host chromosomes at a very low frequency (Nowrouzi, *et al* 2012), (ii) a limited number of AAV 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 AAV into thousands of rodent eyes. Even when we injected AAV vectors intraocularly in a large number of tumour-prone *p53*$^{-/-}$ mice, we found no evidence of malignant transformation of retinal cells (Balaggan, *et al* 2012). In the highly unlikely event that an intraocular tumour does arise, the comprehensive monitoring procedures described in Section 5.4.2.3 of the protocol will enable early detection and thus prompt 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 AAV vectors has not been detected. Similarly, we detected no vector genomes in semen in our previous retinal gene therapy clinical trial (Bainbridge, *et al* 2008). Systemic intravascular administration of rAAV2 to deliver factor IX in haemophilia B, can lead to vector sequences detectable in semen, though not sperm for a short period (Manno *et al* 2006). However, in this instance doses ranging from 8 x 10^{10} to 2 x 10^{12} vg/kg were administered, considerably higher than the doses proposed for subretinal injection in this study. Whilst this indicates there may be some potential for inadvertent germline transmission following the systemic delivery of high doses of vector, 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. To manage the risk of surgical adverse events, only highly experienced surgeons will perform the procedure. Complications of surgery are typically managed effectively by medication or further surgical intervention but can rarely result in lasting harm to sight. The risk of lasting severe impairment of sight from vitrectomy surgery is approximately 1 in 1000. We have identified some reduction in outer retinal thickness and deterioration in acuity in 2 of the 12 participants in our previous clinical trial, believed to result from temporary retinal detachment which is a deliberate consequence of targeted administration of the vector suspension, but no other significant surgical adverse effects.

Delivery of ATIMP to the subretinal space will be performed by standard surgical vitrectomy. This will involve a 3-port pars plana vitrectomy followed by injection of ATIMP using a fine cannula through small retinotomies, resulting in a temporary retinal detachment. Previous gene therapy clinical trials have shown that the bleb of subretinal ATIMP 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.

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 visual function by limiting ATIMP delivery to the area of retina most likely to benefit, and by leaving the contralateral eye untreated. Retinal detachment caused by persistent vector bleb or intraoperative retinal tear is expected to occur in fewer than 1 in 100 procedures and can be effectively managed in the majority by retinopexy, with or without intraocular tamponade. 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 in surgery for subretinal haemorrhage, and an adjunctive technique in the management of retinal detachment.

4.1.5.6 Risk of adverse effects of short-term corticosteroids

Candidates will be screened for contra-indications to 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, as will renal function and liver function (at baseline, 1 day, 7 days, 2 weeks and 4 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 Risk of rod photoreceptor dysfunction

The aim of the intervention is to improve the function of cone photoreceptor cells. Rod photoreceptors exposed to the ATIMP are not expected to benefit but may be subject to adverse effects of the surgical intervention or ATIMP. We plan to minimize any adverse effect by targeting the ATIMP to the central retina where the cone photoreceptors predominate. In addition, the use of a cone specific promoter to drive *CNGB3* expression specifically in cones, will minimise inappropriate ectopic expression in rod photoreceptors. Moreover, should cone photoreceptor-mediated vision be improved by the gene therapy, any dysfunction of rod photoreceptor cells is expected to be evident only in a dimly illuminated environment.

No rod dysfunction has been described to date in the animal models (mouse and dog) used to demonstrate the potential of gene supplementation therapy in *CNGB3*-associated achromatopsia.

4.1.5.9 Risk of thinning of the fovea

Thinning of the retina in the macula (macular thinning) has been detected in 6/10 participants after subfoveal delivery of AAV vector in our previous clinical trial. Macular thinning was typically apparent within 3 months and subsequently non-progressive. Associated thinning of the photoreceptor cell (outer nuclear) layer was evident, with variable disruption of the photoreceptor ellipsoid (inner segment) zone. Participants in the proposed trial may develop macular thinning but since the central macula comprises predominantly cone photoreceptor cells that have no function in achromatopsia, we do not expect this to affect vision adversely.

4.1.5.10 Risk of visual imbalance

Individuals affected by achromatopsia have severe sight impairment with no colour perception from birth. Improvement of retinal function by intervention later in development is expected to lead to new visual experiences. While these are expected to be positive, unpleasant visual sensations might also be experienced.

4.1.5.11 Conclusion on the risk-benefit ratio

In summary, the risks associated with the intervention are justified by the potential for individual participants to benefit, and by the scientific value of the trial to the development of treatments for other individuals similarly affected.

4.1.6 Explanation for Choice of Comparators

There is no currently approved treatment for achromatopsia caused by mutations in *CNGB3*. The comparator will be the contralateral eye.

4.2 Objectives

4.2.1 Primary Objective

The primary research objective is to assess the safety of a AAV2/8 vector for h*CNGB3* gene replacement in the retina. Safety is defined as:

Safety is defined as the absence of 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)

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 6-week period.

4.2.2 Secondary Objective

The secondary research objective is to determine whether a AAV2/8 vector for h*CNGB3* gene replacement in the retina can improve retinal function, visual function and quality of life.

4.3 Trial Design

This is an open-label phase I/II dose-escalation trial to determine the safety and efficacy of subretinal administration of the ATIMP in participants with *CNGB3*-related achromatopsia.

In the dose escalation phase, up to 18 adult participants will be administered a single dose of the ATIMP in cohorts of 3 participants at a time. 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 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.

Once an acceptable safety profile has been established in adults, up to 18 additional participants, who may be children or adults, will be included. The IDMC will agree the maximum tolerated dose in adults before recommending administering up to this dose in the expansion phase.

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

4.3.1.1 Separate longer term follow up study

Safety will be assessed on an ongoing basis in this study. When the 6 months follow up time point has been reached in this study, participants will subsequently be invited to enrol in a separate 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 appropriate if the ATIMP 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 and 6) and in the long-term follow up study (at months 9 and 18). The-follow up study will have a separate protocol, participant information and consent process, and will be submitted for separate ethical review. Participants in the current study will be strongly 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 elect not to participate in the long-term follow-up study; however, in this motivated population, where individuals are typically monitored by their specialist closely and regularly, this is considered unlikely.

4.3.2 IMP administration Review and Dose Escalation Criteria and Process

Up to 18 adult participants (as defined in section 4.3) will be administered a single dose of ATIMP in a total volume of 0.5mL, according to the dose-escalation criteria:

1) low dose [redacted]
2) intermediate dose [redacted]
3) high dose [redacted]

Once a maximal tolerated dose is established, up to 18 further participants aged 3 years or older will continue to be administered vector up to the highest dose observed to be tolerated in adults.

In order to explore optimal dosing within safe limits ([redacted]), additional doses may be administered in order to maximise therapeutic effect, whilst maintaining the safety profile of the product. Any dose that differs from those described above will not exceed the highest titre of [redacted]. The Chief Investigator, Medical Monitor and IDMC chair will confirm additional doses and participant numbers in advance of them being administered. The actual titre to be administered will be recorded in the eCRF.

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 6 weeks of follow up from each cohort of 3 participants, before recommending the next dose to be assessed in a further cohort of patients.

A DLE is defined as any of the below occurring during the 6 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 (defined below)
- Infective endophthalmitis
- Ocular malignancy
- 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 6-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 ATIMP dose recommended by the IDMC, once a safety profile has been established in adult participants according to the dose escalation rules.

4.3.2.2 Dosing process

4.3.2.2.1 Cohort 1

ATIMP will first be administered at the lowest dose to one adult participant only. This participant will be monitored for signs of toxicity for a period of 6 weeks. If there is no DLE as defined above after a minimum of 6 weeks, ATIMP 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 up to 6 weeks following ATIMP 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 ATIMP at the intermediate dose level to a single adult participant. If there is no DLE after a minimum of 6 weeks, ATIMP 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 6 weeks following ATIMP 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 may recommend administering ATIMP at the highest dose level to a single adult participant. If there is no DLE after a minimum of 6 weeks, ATIMP 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 a 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 IDMC are comfortable on review of the accumulating data, to recommend a maximum dose to be administered to children, or 3 participants have been 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 patients 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			
Low dose			
Participants 1-3	**Participants 4-6**	**Action**	**Details**
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 UK II Ltd. will seek IDMC agreement on the highest dose that can be administered in the expansion cohort. This may include up to 18 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 determined 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 ATIMP will be monitored for safety for a period of 6 weeks. If there is no adverse event consistent with the above definition of a DLE after 6 weeks, ATIMP will continue to be administered to up to 17 further participants. In the event of an AE 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 MeiraGTx UK II Ltd. 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. Data will be collected from 3 centres: one in the United Kingdom (UK) and two in the United States (US).

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 this trial of gene therapy for achromatopsia (*CNGB3)*, investigators and trial sites must fulfil a set of criteria that have been agreed by the Clinical Management Team (CMT) as 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 a sufficient number of potential participants to meet their enrolment objectives
- 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 for Achromatopsia (*CNGB3*) 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 Clinical Trial 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 supervise and 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 participants 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) 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 patients 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 Health Research Authority (HRA) 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 trial 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.

5.3.1.2 Participant Inclusion Criteria

Inclusion in the trial will be limited to individuals who:

1. Are aged 3 years or older (children, as defined in Section 4.3 will be enrolled only once the MTD has been determined)
2. Have achromatopsia confirmed by a retinal specialist (CI or PI)

3. Have homozygous or compound heterozygous missense or null mutations in *CNGB3* confirmed in an accredited laboratory
4. Have evidence of relative photoreceptor survival at the macula, which will be assessed by OCT +/- AO
5. Are able to give informed consent or assent, with or without 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 double barrier method of birth control; or abstinence) for at least 12 months following ATIMP administration (Section 4.1.5, Assessment and Management of Risk)
8. If male, are willing to use barrier and spermicide form of contraceptive or maintain sexual abstinence for at least 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

5.3.1.3 Participant Exclusion Criteria

Individuals will be excluded who:

1. Are females who are pregnant or breastfeeding
2. Have uncontrolled gastro-oesophageal reflux or are using non-steroidal anti-inflammatory drugs on a regular basis at the time of screening
3. Have a known allergy to any of the non-investigational drugs to be used in the trial as defined in Section 5.4.1
4. Have participated in another research study involving an investigational medicinal therapy for ocular disease within the last 6 months
5. Have any other condition that the CI/PI considers makes them inappropriate for entry into the trial, inclusive of but not limited to a history of the following:
   hypertension, diabetes mellitus, tuberculosis, renal impairment, immunocompromised state, osteoporosis, gastric ulceration or severe affective disorder
6. Have an ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results
7. Have had intraocular surgery within 6 months of screening
8. 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 be performed only 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 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 patients in the same situation as a usual standard of care. However, results of any procedures that were performed as part of the usual standard care within the screening/baseline window of this study and prior to enrolment on this study may be used for baseline/screening if the subjects 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 an independent counsellor or advisor. Potential participants will be provided with the relevant patient information 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 (noted in their medical notes) or written assent to participation where this is age appropriate (i.e., children aged over 6 years). Children aged over 6 years will be included in the trial only if they assent to participate. 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 re-consented as adults at the time of the 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 routine clinical examination results within 6 months of the screening visit and the subject has consented to allow the use of those tests, then those screening tests will not need to be repeated.

Participants will undergo genetic screening for *CNGB3* 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 state, 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 (includes prescription medications and over-the-counter preparations) used by the patient from enrolment date, during the study, and at the study drug discontinuation visit will be documented and recorded on eCRF.
3. Physical examination
4. Vital signs including blood pressure
5. Ocular examination
6. Visual acuity
7. Contrast sensitivity
8. Spectral Domain Optical Coherence Tomography (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 6 months prior to enrolment. In addition, females of childbearing 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 6 months of enrolment. If the ATIMP is not delivered within 6 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 Intervention

5.4.1 Name and Description of Investigational Medicinal Product

AAV2/8-hCARp.hCNGB3 is an advanced therapy investigational medicinal product: specifically, a gene therapy product.

AAV2/8-hCARp.hCNGB3 is a gene transfer agent to be developed for the treatment of a form of achromatopsia caused by defects in the gene encoding *CNGB3*. This is the beta subunit of the cGMP-gated ion channel that plays an essential role in the cone phototransduction pathway. Disruption of the gene prevents the conversion of light to an electrical signal, leading to lack of cone function and visual dysfunction. Recombinant adeno-associated virus (rAAV) mediated gene transfer of a copy of the normal *CNGB3* gene to the cone photoreceptors, results in stable, long term transgene expression and improves visual function significantly in both rodents and dogs with *CNGB3* gene defects

AAV2/8-hCARp.hCNGB3 consists of a linear single strand of DNA packaged in a rAAV protein capsid of serotype 8. The AAV2/8-hCARp.hCNGB3 genome incorporates 290 nucleotides of the wild-type AAV2 ITR (Inverted Terminal Repeats) sequences that provide *in cis* the packaging signal, a cDNA encoding human *CNGB3*, a human cone-specific genomic promoter (cone arrestin, CAR) and a SV40 (simian virus 40) polyadenylation signal. The icosahedral capsid consists of three related capsid proteins, VP1, VP2, and VP3. AAV has a compact macromolecular structure and forms stable viral particles 20nm in diameter. The vector particles are replication incompetent.

5.4.1.1 ATIMPs Classified as Genetically Modified Organisms

The ATIMP (AAV2/8-hCARp.hCNGB3) 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 participants. Trial sites that receive support for recombinant or synthetic nucleic acid molecule research from the National Institutes of Health (NIH) must register the protocol with the NIH Office of Science Policy (OSP) for review prior to initiating trial activities.

5.4.1.2 Source of ATIMPs

The ATIMP has been manufactured at the [redacted] in accordance with current Good Manufacturing Practice for clinical trial materials. The product is released by an EU QP.

5.4.1.3 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.

The ATIMP is a recombinant serotype 2/8 adeno-associated viral vector containing a human *CNGB3* cDNA driven by a 0.4 kb fragment of the human CAR promoter.

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 ATIMP 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.

5.4.1.4 Description and Justification of Route of Administration and Dose

Efficient transduction of the cone photoreceptor cells requires the ATIMP (rAAV2/8-hCARp.hCNGB3) to be administered to the subretinal space.

Delivery of vector suspension to the subretinal space will be performed by 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 into the subretinal space, resulting in a transient 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 ATIMP delivery, and by leaving the contralateral eye untreated. Injection of fluids under the retina is less commonly performed but is a standard step for delivery of surgical dyes and in surgery for macular degeneration performed at [redacted] and elsewhere.

The highest ATIMP dose that is intended to be delivered to the trial participants is based on dose-limiting toxicity that was seen in an earlier trial of AAV2-mediated gene therapy for LCA2, where 1 mL of ATIMP at [redacted] was found to be the highest safe dose that could be administered subretinally. As toxicity in this context is a complex interaction between local retinal effects, wider ocular effects and systemic effects, a conservative decision was taken to use the confirmed safe titre ([redacted]), despite using a smaller maximal volume (0.5 mL) and thus a slightly lower dose. As AAV2/8-mediated transduction of cone photoreceptors in non-human primates is efficient over a wide range of titres, including much lower titres than used in this study (Vandenberghe *et al*, Sci Transl Med 3, 88ra54) we are confident that the *CNGB3* transgene can be delivered to the cones effectively at [redacted].

5.4.1.5 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 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 4 weeks
- In children aged up to 16 weighing 5 kg to less than 10 kg (11 lb to less than 22 lb): 5 mg taken once per day
- In children aged up to 16 weighing 10 kg to less than 20 kg (22 lb to less than 44 lb): 10 mg taken once per day
- In children aged up to16 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:

0.5 mg/kg daily for one week **prior** to ATIMP administration
1mg/kg daily for the first week following ATIMP administration
0.5mg/kg daily for the second week following ATIMP administration
0.25mg/kg daily for the third week following ATIMP administration
0.125mg/kg daily for the fourth week following ATIMP administration

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

A detailed 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 6-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 as a part of routine clinical examination within 6 months. 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 assessment results will be sent for reading and analysis to independent reading centres within the UK and US. For both sites imaging with OCT, fundus autofluorescence and fundus photography will be reviewed by the site teams but also sent for independent analysis by the [redacted], during the course of the trial. Adaptive optics images will be sent to the [redacted] for reading and Octopus perimetry and Microperimetry will be sent to the [redacted] 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 remain unidentified.

Up to 10 mL of blood will be sampled in order to assess baseline levels of circulating antibodies against, AAV8 and of circulating antibodies against rAAV serotype 8 so that immunological responses to vector capsids can be determined following ATIMP administration (collectively described as serology in Table 2: Trial Assessments). We anticipate that that majority of participants will have no detectable pre-existing circulating antibodies against AAV8. The presence or absence of circulating antibodies will not affect recruitment of the participant. All serology tests will be performed at the Institutional Laboratory in the UK.

There is wide variability in the abilities of individual children to perform certain of the proposed investigations; the evaluations for children will be restricted to those tests that individuals are able to perform reliably.

Tests that will be performed in all participants are:

- Serological tests
- Blood pressure
- Haematology
- Biochemistry
- Ocular examination
- Colour fundus photography
- Spectral Domain Optical coherence tomography (SD-OCT)
- Fundus Autofluorescence (FAF) imaging
- Best corrected visual acuity
- Full-field electroretinography (ERG)
- Pattern electroretinography (PERG)

Tests that will be performed where possible are:

- Contrast sensitivity
- Reading assessment
- Static perimetry
- Colour vision testing
- Light-sensitivity testing
- QOL questionnaire

Further details of clinical assessments can be found in the Gene Therapy for Achromatopsia (*CNGB3*) study manual. Images taken at all timepoints will be sent for independent reading and analysis at centres in both the UK and US.

(i) Ocular examination and retinal imaging.

Ocular examination using slit lamp biomicroscopy will assess the anatomical integrity of the eyes and allow quantification of intraocular inflammation. During the examination, intraocular pressure will be determined by tonometry.

Retinal imaging includes colour fundus photography, fundus autofluorescence (FAF) imaging and SD-OCT. 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.

(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 questionnaire and EQ5D-Y questionnaire.

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

The degree of light sensitivity (photoaversion) will be investigated in two ways (i) Objectively by measurement of palpebral aperture narrowing in response to gradually increasing light intensity and (ii) Subjectively by participant reported symptomatology.

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

Colour vision will be assessed comprehensively using plate tests and computerised tests probing colour discrimination along all 3 axes of colour.

Retinal sensitivity will be determined using static perimetryand full field stimulus testing (FST) where available. FST may be performed for enrolled patients at participating sites. The retinal locus of fixation will also be determined using microperimetry.

Full-field electroretinography (ERG) and pattern ERG (PERG) will be performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards to assess both generalised retinal (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 defining ISCEV standards.

5.4.2.2 ATIMP administration Procedures

The protocol describes the intended surgical technique for ATIMP administration. The surgical procedure may be modified on a case-by-case basis in the interests of safety; any modification will be documented in the operation notes and eCRF. Consent to record the surgery will be requested of the participant. Intraocular surgery will be recorded by video via the operating microscope as described in the consent process. Relevant video recordings and images will be stored alongside the trial database.

5.4.2.2.1 Pre-operative Procedures

For prophylaxis against potential intraocular immune responses to the ATIMP, participants will be prescribed a course of oral prednisolone, commencing at a daily dose of 0.5 mg/kg one week prior to ATIMP administration; 1mg/kg for the first week following administration, 0.5mg/kg for the second week, 0.25mg/kg for the third week and 0.125mg/kg for the fourth week.

Preoperative procedures and intraocular administration of ATIMP will be as described in the Gene Therapy for Achromatopsia (*CNGB3*) study manual.

5.4.2.2.2 Technique for intraocular administration of ATIMP

The choice of eye for ATIMP administration will be the poorer-seeing eye as identified by the participant and CI/PI taking into account ocular dominance and visual acuity.

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 include a 3-port pars plana vitrectomy followed by injection of ATIMP using a fine cannula through small retinotomies into the subretinal space.

Surgery will be performed under general anaesthesia. The eye and face will be prepared using povidone iodine solution as per routine intraocular surgery. 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. Three pars plana sclerotomies will be sited to enable intraocular infusion, endoillumination probe and surgical instruments. The fundus will be viewed by means of a binocular indirect ophthalmo microscope (BIOM) indirect viewing system or a contact lens. To minimise the possibility of unplanned retinal detachment or preretinal fibrosis, vitrectomy (aspiration of vitreous gel) will be performed using a disposable cutter.

Intraocular administration of the viral vector suspension (AAV2/8-hCARp.hCNGB3) will be performed using a subretinal cannula advanced through the retina.

Under direct visualisation, the ATIMP will be injected under the neurosensory retina, causing a localised retinal detachment with a self-sealing non-expanding retinotomy. The aim will be to target the ATIMP to the central macula. If appropriate, the bleb of ATIMP will be manipulated to the target area using a fluid-air exchange. The site and extent of the subretinal bleb of ATIMP suspension will be documented by video recording.

Following intraocular administration of ATIMP, the retinal periphery will be examined for any unplanned retinal breaks for appropriate management by retinopexy with or without intraocular tamponade at the discretion of the operating surgeon. Intraocular instruments used subsequent to ATIMP delivery are disposable and will be destroyed after a single use. Sclerotomies may be secured using a vicryl suture. Standard doses of cefuroxime antibiotic and betamethasone will be administered subconjunctivally as prophylaxis against postoperative infection and inflammation respectively. Bupivacaine will be administered for analgesia. The surgical procedure may be modified on a case-by-case basis in the interests of safety; any modification will be documented in the operation notes and CRF.

On the basis of our own experience, we anticipate that the subretinal ATIMP bleb will resolve spontaneously during the first 48 hours.

Surgery may be performed, as is conventional for intra-ocular procedures, on a day-case basis and participants will be managed subsequently as out-patients, although hospital-based accommodation may be used for convenience.

5.4.2.3 Subsequent Assessments

On the first postoperative day a full clinical ocular examination will be performed. In particular, visual acuity, intraocular pressure, the degree of postoperative intraocular inflammation and the area of any residual retinal bleb will be documented. Fundus photography, autofluorescence imaging, ocular examination, intraocular pressure and SD-OCT will be performed at day 1 and each subsequent visit post ATIMP administration.

A standard post-vitrectomy treatment regimen of topical antibiotic (chloramphenicol 0.5% qds for 7 days) and steroid (dexamethasone 0.1% qds for 4 weeks) will be prescribed 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 4 weeks following administration of ATIMP as described above (Section 5.4.2.2.1: Pre-operative procedure). The possible development of steroid-induced adverse effects will be monitored regularly. In particular, blood pressure will be measured and blood glucose, renal function and liver function will be evaluated through blood biochemistry at the time points specific in Table 2: Trial Assessments.

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

(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 expected 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+ cells) intensity. The degree of intraocular inflammation is expected to decline over the course of the first 4 weeks following the surgical procedure, at which time the routine topical and systemic immunosuppression will be discontinued. Prolonged or severe intraocular inflammation, or deterioration in visual acuity that may be related to intraocular inflammation, will be investigated and managed conventionally with further topical and/or systemic immunosuppression.

(ii) **Evaluation of immune responses**

Up to 10 mL of blood will be sampled to measure immune response. Antibody responses to AAV capsid proteins will be investigated by ELISA at baseline and at 4 weeks, 3 months, and 6 months following ATIMP administration.

(iii) **Evaluation of biodistribution**

Systemic biodistribution of vector genomes will be assessed by PCR analysis of tears a compressed cellulose sponge placed under the eye lid until swollen), saliva (a minimum of 100 µL) and serum (1 mL) at 1 day and at 4 weeks following intraocular ATIMP administration. The test will be carried out in the [redacted].

(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). They will be carried out with the same methods applied for the baseline tests (see section 8.6 for details) to allow direct comparison of the data sets. These assessments will be scheduled over a period of a day for visits at day 1, day 3, day 7, week 2, week 4 and week 6 after surgery, and up to 4 days for baseline examinations, and 3 months, 6 months following ATIMP administration. 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 reliable visual acuity testing and SD-OCT imaging, which are the principal clinical assessments both for safety and efficacy. Other clinical assessments will be undertaken as appropriate for the ability of individual participants, since there is wide variation in the abilities of individual children to perform such tests reliably; the evaluations for individuals may be restricted to those tests that they are able to perform reliably.

Additional assessments may be performed if considered appropriate for the management of any unexpected adverse effects. These may be submitted as urgent safety measures and protocol amendments performed where required. Conversely, tests that cannot be reliably performed by a particular participant may be discontinued for that participant. This is not anticipated for the key clinical assessments such as visual acuity test or SD-OCT imaging because participants who are unable to perform such tests will be excluded from the study at the screening phase. Evaluation of safety and efficacy will also be performed on an individual participant basis. We do not anticipate that any discontinuation will affect significantly the overall quality of the safety and efficacy evaluation.

5.4.2.4 Laboratory Procedures

Blood serum will be processed within [redacted] to investigate any immune responses to the ATIMP:

1. anti-AAV8 neutralising antibodies
2. anti-AAV8 antibodies using an ELISA

Blood serum, saliva and lacrimal fluid will be processed in the [redacted] to assess dissemination of ATIMP after delivery, where the number of rAAV vector genome copies will be measured using a polymerase chain reaction (PCR) approach.

Whole blood will be processed at the [redacted], or a CLIA-accredited molecular diagnostic laboratory in the US, for *CNGB3* mutation screening. Haematology and biochemistry samples and screen will be carried out at the Trust associated laboratories, or an accredited laboratory in the US.

5.4.3 Dispensing

5.4.3.1 Receipt and Storage of the Advanced Therapy Investigational Medicinal Product

The batch of ATIMP will be stored at either the [redacted] or other approved storage facility (details of storage will be specified in the ATIMP Management Plan).

The product, which is stable at ≤–50° Celsius, will be stored at -70° Celsius or below in secure temperature controlled and monitored -80° Celsius freezers. No further manufacturing or testing will take place at the [redacted]. Shipping of ATIMP will be on dry ice, accompanied by a temperature-monitoring device.

The ATIMP vector will be dispensed on the same day of administration according to study specific working instructions, with a 1-hour window for administration after ATIMP has thawed at room temperature.

5.4.4 Dosages

5.4.4.1 Dosages and dosage modifications

Trial participants will receive a single dose of ATIMP within the range proven to be safe in the preclinical animal studies. These are anticipated to be as described below:

1) low dose [redacted]
2) intermediate dose [redacted]
3) high dose [redacted]

In order to explore optimal dosing within safe limits ([redacted]), additional doses may be administered in order to maximise therapeutic effect, whilst maintaining the safety profile of the product. Any dose that differs from those described above will not exceed the highest titre of [redacted]. The Chief Investigator, Medical Monitor and IDMC chair will confirm additional doses and participant numbers in advance of them being administered. The actual titre to be administered will be recorded in the eCRF.

The ATIMP will be produced and stored at a titre appropriate for the high dose ([redacted]) and diluted immediately prior to intraocular administration in Hartmann's solution at the time of administration for lower doses. The CI/PI will prepare the appropriate dilution and this will be checked in the operating theatre by a second individual prior to administration. The check will be recorded in the patient's source data notes.

Further details for dose-escalation criteria are included in Sections 5.3.2.

5.4.5 Accountability

The ATIMP will be prescribed for a particular participant by one 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
iii. batch number
iv. volume and dose of ATIMP administered
v. name of Principal Investigator 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 participant and destruction or final disposition. A comprehensive ATIMP management plan and associated Working Practices 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

Intraocular administration of the ATIMP will be performed by the operating surgeon (CI or a delegated vitreo-retinal surgeon). The volume of ATIMP delivered to the target site will be measured from the scale located on 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 participant 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 Participant Withdrawal

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

As participation is entirely voluntary, participants may choose to withdraw from the trial at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for withdrawal, a reasonable effort should be made to establish and document this in the withdrawal eCRF, whilst fully respecting the participants rights.

Should a participant withdraw from the study, a withdrawal eCRF documenting the reason for withdrawal (if provided) will be completed, in addition to the procedures and eCRF 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 ATIMP administration will be regarded as off-protocol and their primary ophthalmologist will resume normal standard of care. Any participant who withdraws prior to administration of ATIMP may be replaced in the study.

Participants who withdraw from the study after ATIMP administration will be strongly encouraged to have follow-up investigations with their consent, so that the consequences of ATIMP administration can be documented and the data analysed. The CMT may choose to replace a participant who withdraws after ATIMP 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 severe adverse event 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 study
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 6 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.

- Any improvements in visual function from baseline that are greater than the test-retest variation and are sustained for at least two consecutive assessments.
- Any improvement in retinal function from pre – intervention that is greater than test-retest variation and measurable by electrophysiology (pattern ERG, multifocal ERG or full-field ERG). Quality of life will be measured by the Impact of Visual Impairment (IVI) questionnaire and the EQ5D-5L and EQ5D-Y.

5.6 Trial Assessments

Table 2: Trial assessments

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

	Screening	Baseline[1,]			ATIMP admin	D1	D3	W1	W2	W4	W6	W12	W24
Flexibility of schedule (± days)		- 6 months			Day 0	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 14D	± 14D
Fundus photography		●				●	●	●	●	●	●	●	●
Optical coherence tomography	●	●	●	●		●	●	●	●	●	●	●	●
Adaptive optics imaging		●	●										●
Fundus autofluorescence		●	●									●	●
Pattern Electroretinography[,4]	●												●
Full field Electroretinography[,4]	●												●
Photoaversion assessments		●[5]	●[5]	●[5]								●	●

[1] Baseline assessments may be performed on the same day where considered logistically and clinically appropriate

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

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

[4] ERG assessments may be performed under general anaesthesia if considered appropriate

[5] Photoaversion Questionnaire only to be completed at one baseline visit

[6] Not required to be repeated if previous result available from an accredited laboratory

5.6.1 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, 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, and the participant withdrawn entirely from the trial. MeiraGTx UK II Ltd. should be informed of the withdrawal. 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 regard 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 and FDA will be notified of the end of the trial within 90 days of its completion.

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

At the end of this trial, participants will be invited to enrol in a follow-up study to determine the longer-term safety and efficacy up to 60 months' post treatment administration.

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 36 participants (up to 18 in the dose escalation phase and up to a further 18 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 36 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 [redacted], or the [redacted] or on referral by ophthalmologists within or outside the UK or 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. Potential participants may also contact the trial team independently. We expect to recruit up to 36 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 AAV2/8-hCARp.hCNGB3 to one eye. The dose received by each participant will depend on the time/order of their enrolment in the trial according to the sequence of dose escalation, and the extent of dose limiting events (see sections 4.3.2 and 5.4.4 for dose escalation information). Children will be enrolled in the trial only once 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

[redacted] 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 [redacted].

[redacted] 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. [redacted] 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.

5.10.2 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. Data collected prior to withdrawal will be considered 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.

5.10.3 Statistical Methods

5.10.3.1 Statistical Analysis Plan

A formal Statistical Analysis Plan (SAP) will be written by the 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.

5.10.3.2 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 6 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)

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

It is anticipated that the ATIMP will be administered at the MTD in up to 15 participants (6 adults in the dose escalation phase and up to 18 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.

5.10.3.3 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 than 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 test-retest variation and measurable by electrophysiology (pattern ERG, multifocal ERG or full-field ERG).

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 IDMC and described in the final report, as appropriate.

5.10.3.4 Statistical Methods – Health Economics Analysis

No health economic evaluation is planned, but the collection of EQ5D would allow Quality Adjusted Life Years (QALYs) to be calculated.

5.11 Data Monitoring

5.11.1 Independent Data Monitoring Committee

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 changes in the dose escalation phase, and prior to the enrolment of the first participant in the dose expansion phase.

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 *CNGB3* Gene Therapy Trial for Achromatopsia 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 IDMC charter.

5.11.3 Data Monitoring for Harm

5.11.3.1 Safety reporting

[redacted] 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 (eg 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 one 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 ATIMP, all safety events will be reviewed within a short time frame for all participants, as described in the *CNGB3* Gene Therapy Trial for Achromatopsia 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 [redacted] on a pregnancy report form within 24 hours of the investigator becoming aware of the event. The participant will continue to be assessed 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 this 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 [redacted] on a pregnancy report form within 24 hours of the investigator becoming aware of the event.

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, whether expected or not, should be recorded in the participant's medical notes, including all events observed following ATIMP administration, and in eCRF. These should be entered on to the database according to the timelines defined in the *CNGB3* Gene Therapy trial for Achromatopsia Data Management Plan to allow appropriate monitoring by the CMT. SAEs and SARs should be notified to [redacted] immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

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 eCRF. 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 Table 3. If the event is classified as 'serious' an SAE form must be completed and emailed to [redacted] (or delegated body) 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 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. If the event is related to the ATIMP, definitions in Table 5 will be used to capture the information. Any event that is only related to the ATIMP administration surgery will be classified as an Adverse Event.

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 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 is not expected to cause undue discomfort. 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 (to hand movements or better for a period of up to 8 weeks), 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 [redacted]

All adverse events will be recorded in the hospital notes and the eCRF from the date of written informed consent until last study visit.

Investigators should notify [redacted] of any SAEs and SARs occurring during this period. After the 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.

[redacted] must be notified of all SAEs and SARs within 24 hours of the investigator becoming aware of the event. The investigator will respond to any SAE queries raised by [redacted] 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 and causality 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 [redacted]. 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 [redacted]

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 [redacted] as further information becomes available. Additional information and/or copies of test results etc 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 should be blacked out and replaced with trial identifiers on any test results if it is displayed. Such instances must also be reported to the CMT.

5.11.3.6.2 Reporting Urgent Safety Measures

MeiraGTx UK II Ltd. 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 the CI/PI/ MeiraGTx UK II Ltd. shall immediately (no later than 3 days from the date the measures are taken), give written notice as per local reporting

requirements of the measures taken and the circumstances giving rise to those measures, according to the relevant SOP.

5.11.3.6.3 [redacted] responsibilities

[redacted] will follow [redacted] Standard Operating Procedures and a study specific Safety Management Plan to ensure that case processing of events occurs within appropriate regulatory timeframes. [redacted] 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 *CNGB3* Gene Therapy trial for Achromatopsia are based on 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 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must 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 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 trial 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 study conduct and data review) and authority will be covered in a CMT terms of reference.

5.11.4.4.2 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to 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 charter. The IDMC will consider data in accordance with the statistical analysis plan and will advise the CMT.

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 Health Research Authority (HRA) for approval. Any subsequent amendments to these documents will be submitted for further approval.

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. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

6.2 Regulatory 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 departments of each participating sites. A copy of the local approval letter (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. If a child becomes an adult during their participation in the trial, the child will be reconsented as an adult at the time of their next scheduled visit.

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 the MeiraGTx UK II Ltd. trial team.

6.6 Confidentiality

All data will be handled in accordance with the General Data Protection Regulation 2016/679 or the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

These regulations require a signed participant 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 participant 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 participant 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 participant 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 participant 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 participant, except as necessary for trial-related monitoring, audits, REC/IRB review, and regulatory inspections by University or government entities. In these 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 MeiraGTx UK II Ltd.

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

For other information regarding Data Management please see Section 5.10.2.

6.7 Declaration of Interests

The trial is funded by MeiraGTx UK II Ltd.

[redacted] declares ownership of minority shareholdings in MeiraGTx UK II Ltd. and receipt of payment from MeiraGTx UK II Ltd. for consultancy services.

[redacted] declares ownership of minority shareholdings in MeiraGTx UK II Ltd. and receipt of payment from MeiraGTx UK II Ltd. 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.

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 trial is fully funded by MeiraGTx UK II Ltd. It is not expected that any further external 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 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
- Participant 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 [redacted] 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 MeiraGTx UK II Ltd.

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 Protocol Amendments

Protocol Version and Date	Reason for Amendment
Protocol v1.0 dated 15 Jul 2017	Initial version
Protocol v2.0 dated 3 Mar 2017	relevant changes in the operational responsibilities of the study.
Protocol v3.0 dated 09 Oct 2017	Safety reporting clarification, Dose expansion clarifications
Protocol v4.0 dated 01 May 2018	To clarify the allowance of data obtained from the usual standard of care be used for screening and or baseline assessments (with consent from subjects) in order to avoid unnecessary testing of subjects and also to extend the screening/baseline window from 3 months to 6 months. Clarify that more than 1 surgeon at a site may inject vector To remove CI will confirm eligibility of all individual participants To add FST as a visual assessment Expand the number of categories for ATIMP administration surgery from related or unrelated to: unrelated, unlikely, possibly, probably or definitely

	To clarify ATIMP vector must be administered with a 1 hour window after ATIMP has thawed at room temperature.
Protocol v5.0 dated 05 Dec 2018	To increase the number of participants to be recruited in the dose expansion phase and to allow for additional doses of vector to those described to be explored.
Protocol v6.0 17 Dec 2018	Addition of wording to provide clarification regarding what is considered “safe limits”
Protocol v7.0 29 Jan 2019	Updated to remove assessments that have been reviewed and deemed to add no scientific value to continue testing, in order to reduce assessment burden to participants and clinical sites.

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