Gene Therapy for Achromatopsia (*CNGA3)*

An open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV8-hG1.7p.coCNGA3) for gene therapy of children with Achromatopsia owing to defects in *CNGA3*

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Sponsor	MeiraGTx UK II Ltd.
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Trial registration	EudraCT 2018-003431-29

Authorisation: Chief Investigator

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Date	

Authorisation: Sponsor Representative

Name	[redacted]
Role	MeiraGTx Chief Medical Officer
Signature	
Date	[redacted] 16-Apr-2021 | 16:13 BST

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1 Administrative information

This document describes the Gene Therapy for Achromatopsia (*CNGA3*) trial, sponsored and co-ordinated by MeiraGTx UK II Ltd. In early 2019, MeiraGTx UK II Ltd. (MeiraGTx) entered into a worldwide collaboration and license agreement with Janssen Research and Development, LLC (JRD), which is based in the US. The partnership seeks to develop, manufacture, and commercialize gene therapy treatments for inherited retinal diseases (IRDs). MeiraGTx and JRD are collaborating on the development of AAV8-hG1.7p.coCNGA3 formerly known as AAV2/8-hG1.7p.coCNGA3.

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 Regulations 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 2018-003431-29
Secondary Identifying Numbers	MeiraGTx UK II Ltd. registration number: MGT012
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] Chief Medical Officer (MeiraGTx) 450 East 29th Street 14th Floor New York, NY 10016 Tel : 646-869-7379 Email : [redacted]
Public Title	Gene Therapy for Achromatopsia (*CNGA3*)
Scientific Title	An open label, multi-centre, Phase I/II dose escalation trial of an adeno-associated virus vector (AAV8-hG1.7p.coCNGA3) for gene therapy of children with Achromatopsia owing to defects in *CNGA3*
Countries of Recruitment	United Kingdom, United States of America
Health Condition	Achromatopsia
Intervention(s)	Open label, non-randomised, dose-escalation [redacted] Phase I/II dose-escalation study, by subretinal administration of AAV8-hG1.7p.coCNGA3 in up to 18 paediatric participants with Achromatopsia owing to mutations in the *CNGA3* gene.
Key Inclusion and Exclusion Criteria	Key Inclusion Criteria: • Aged 3 to 15 years old • Achromatopsia caused by mutations in *CNGA3* • Evidence of relative 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 Advanced Therapy Investigational Product (ATIMP). Key Exclusion Criteria: • Female adolescents who are pregnant or breastfeeding • Intra-ocular surgery within 9 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 • Use of high dose regular non-steroidal anti-inflammatory drugs at the time of screening • Have any other condition that the Principal Investigator (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 • During the 6 weeks prior to baseline, have had any confirmed SARS-CoV-2 (COVID-19) infection
Study Type	Phase I/II, open-label, non-randomised, multi-centre, dose escalation study, followed by dose confirmation in children with Achromatopsia owing to defects in *CNGA3*
Date of First Enrolment	Anticipated Q1 2019
Target Sample Size	Up to 18 participants
Primary Outcome(s)	The primary outcome is safety of subretinal administration of AAV8-hG1.7p.coCNGA3. Safety is defined as the absence of ATIMP-related: • Reduction in visual acuity by 15 ETDRS letters or more that fails to resolve to within 15 letters of baseline in a 4-week period once prophylactic treatment commences • 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 optional 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 baseline 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 baseline variation and measurable by electroretinography (ERG). 3) Quality of life measures including EQ-5D and IVI or equivalent as appropriate.

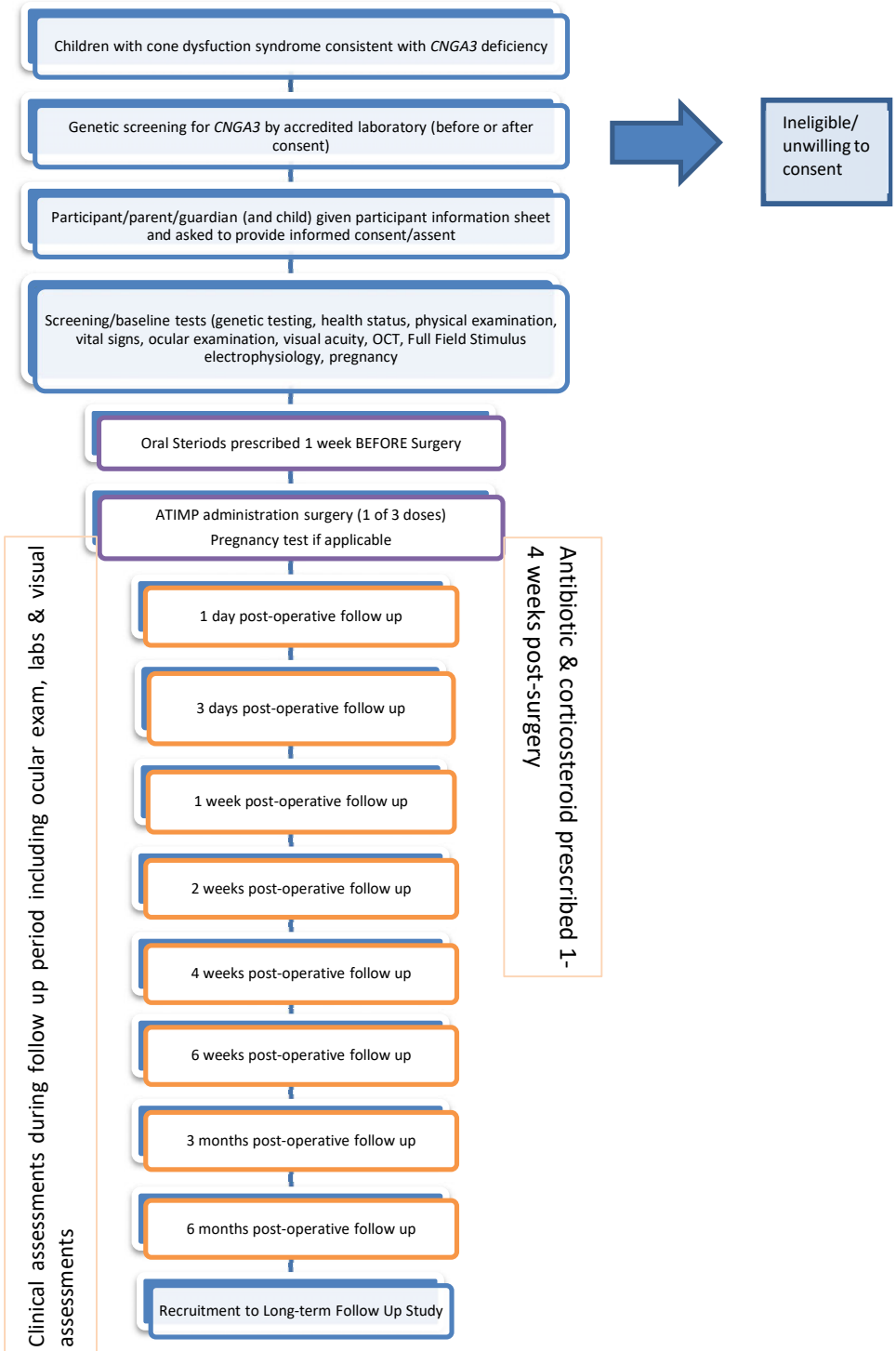
1.4 Roles and responsibilities

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.

Name	Affiliation	Role and responsibilities
[redacted]	University College London	Chief Investigator, Moorfield's Eye Hospital
[redacted]	University College London	Co – Investigator, Moorfields's Eye Hospital
[redacted]	University College London	Senior Scientist
[redacted]	MeiraGTx UK II Ltd.	Chief Medical Officer
[redacted]	MeiraGTx UK II Ltd.	Chief Development Officer
[redacted]	MeiraGTx UK II Ltd.	Senior Director Clinical Operations
[redacted]	MeiraGTx UK II Ltd.	Clinical Project Manager

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
CNGA3	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
ISe	Inner Segment Ellipsoid
SDMC	Safety andData 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
KEC	Kellogg Eye Centre
LCA	Leber congenital amaurosis
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
UCL	University College London
UK	United Kingdom of Great Britain & Northern Ireland
US	United States
vg	Viral Genomes
WGTU	Wolfson Gene Therapy Unit
WT	Wild type

4 Introduction

4.1 Background and Rationale

4.1.1 Background

Achromatopsia is a hereditary autosomal recessive condition characterized by intact rod function and absent cone function. As a consequence of loss of cone function in the retina, Achromatopsia patients present with reduced or complete loss of colour vision, reduced visual acuity, involuntary back-and-forth eye movements (pendular nystagmus), a disabling increase in sensitivity to light (photophobia), and a central scotoma (Kohl *et al.*, 2013; Aboshiha *et al.*, 2016; Michaelides *et al.*, 2004). In the United States, ACHM is estimated to affect approx. 9,700 individuals (Judd, 1943; Sharpe *et al.*, 1990; Sharpe *et al.*, 1999), in 25%-35% of whom the condition results from mutations in the *CNGA3* gene (Kohl *et al.*, 2005; Aboshiha *et al.*, 2016); similarly, it is estimated that approximately 4,000 people are affected in the EU.

There is currently no treatment for any form of ACHM, including forms of the disease due to mutations in the *CNGA3* gene. Among a variety of novel therapeutic strategies that are under investigation for hereditary retinal disorders, such as ACHM, gene therapy has been shown to be most promising, with notable successes in models of inherited retinal dysfunctions owing to loss-of-function mutations in genes encoding proteins that mediate critical functions in photoreceptors or retinal pigment epithelium cells.

In recent years, adeno-associated virus (AAV) has emerged as one of the most efficient viral vectors for gene therapy (Daya and Berns, 2008). Subretinal administration of AAV2/8 vector in the mouse eye shows a substantially higher efficacy of photoreceptor cell transduction, relative to AAV2 and AAV2/5 (Allocca *et al.*, 2007, Natkunarajah *et al.*, 2007). Comparison of multiple AAV serotypes after subretinal injection in the eyes of non-human primates (NHPs) showed AAV2/8 to be among the most efficient vectors for gene transfer to the primate cones (Vandenberghe *et al.*, 2013, Vandenberghe *et al.*, 2011).

Achromatopsia resulting from mutations in *CNGA3* has several characteristics that make it an appropriate 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 children 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 a range of ages will be included.

4.1.2 Pre-clinical data

In unpublished nonclinical study using a murine model of *CNGA3*-deficiency, delivery of a functional copy of the h*CNGA3* cDNA sequence to the cone photoreceptors of Cnga3-deficient mice was associated with significant improvement in retinal function evident on electroretinography (ERG). Subretinal injection of AAV8-hG1.7p.coCNGA3 of 1.0 x 10^{12} vg/mL in mice aged post-natal day 15 (a dose of 4 x 10^{9} vg/eye) led to long-term rescue of ERG responses that persisted up to the last tested timepoint (20 weeks) and a clear dose-dependent effect on ERG restoration was seen using viral titres planned for the proposed Phase I/II clinical trial.

In a further unpublished study, administration of AAV8-hG1.7p.coCNGA3 was associated with a marked increase in cone-cell survival and synaptic integrity in treated eyes when compared to untreated eyes at 11 months. This study constitutes one of the most effective rescues of an animal model of a photoreceptor defect reported to date, suggesting that this defect may be particularly amenable to gene supplementation therapy.

The efficacy and safety of AAV8-hG1.7p.coCNGA3 is also the subject of an ongoing 8-week toxicology and biodistribution rodent study and ongoing 6-month long term gross and ocular toxicity rodent study. In addition, a series of nonclinical pharmacology and toxicology/biodistribution studies have been conducted with a closely related vector (AAV2/8-hCARp.hCNGB3) containing the human CNGB3 gene. As this vector is comprised of the same vector backbone and capsid (serotype 8) as AAV8-hG1.7p.coCNGA3 (albeit with a different promoter and transgene), these data are considered relevant, supportive and representative of the nonclinical programme for AAV8-hG1.7p.coCNGA3.

4.1.3 Clinical data

No clinical studies using AAV8-hG1.7p.coCNGA3 have been conducted to date in any country. However, proof-of-principle for gene replacement therapy in the retina has been demonstrated using recombinant adeno-associated virus serotype 2 (rAAV2/2) vectors delivering the retinal pigment epithelium-specific protein 65 (*RPE65*) gene in several completed clinical trials in Leber Congenital Amaurosis (LCA2) patients (Bainbridge *et al.*, 2008; Maguire *et al.*, 2008; Cideciyan *et al.*, 2009; Russell *et al.*, 2015; Russell *et al.*, 2017).

In these studies, adults and children as young as 6 years of age were administered AAV vectors by subretinal administration, using analogous methods (but with differing doses and volumes) to those proposed for the planned clinical study, at viral doses ranging from 1.5×10^{10} vg/eye to 1×10^{12} vg/eye, with injection volumes ranging from 0.15 to 1 mL. In one of these clinical studies the vector was delivered by subretinal administration that in many cases encompassed the fovea (Bainbridge *et al.*, 2008).

This protocol describes MeiraGTx's 5th clinical trial of a gene supplementation therapy for inherited retinal disease using a recombinant AAV (rAAV) vector.

We are currently investigating the safety and potential efficacy of new optimized vectors in trials with a similar design and protocol to this proposed trial:

- In MGT003 we are investigating an optimized rAAV2/5 vector for delivery of *RPE65* to adults and children with Leber Congenital Amaurosis caused by mutations in *RPE65* (Chief Investigator: [redacted])
- In MGT006 we are investigating an rAAV2/8 vector for delivery of *CNGB3* to adults and children with Achromatopsia caused by mutations in *CNGB3* (Chief Investigator: [redacted])
- In MGT009 we are investigating an rAAV2/5 vector for delivery of *RPGR* to adults and children with X-linked Retinitis Pigmentosa caused by mutations in *RPGR* (Chief Investigator: [redacted])

Notably we will be using the same serotype in the trial herein for CNGA3 (AAV2/8) as has been used in our completed human clinical trial for CNGB3 (AAV2/8). We administered AAV8 vector to 23 participants in total (11 adults and 12 children). A total of 3 serious adverse events (SAE's) were reported in the CNGB3 study, 2 of which were considered at least possibly related to ATIMP. These were unexpected and were, therefore, reported as suspected unexpected serious adverse reactions

(SUSARs). They are further discussed in section 4.1.5. Overall, we judge that the safety profile supports the use of AAV8 vector for children in this trial for CNGA3, given that children are more likely to benefit than adults.

4.1.4 Rationale

In *CNGA3*-related Achromatopsia, delivery of a cDNA sequence encoding a functional CNGA3 protein using gene supplementation could 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 *CNGA3* gene encodes the alpha subunit of the cone photoreceptor-specific cGMP-gated cation channel, which is critical for cellular responses to light. Absence of this alpha 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 *CNGA3* 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 into the dose escalation phase of the study to provide the greatest opportunity for benefit. The totality of the data from paediatric subjects enrolled in the UK and adult subjects enrolled in the U.S. in this dose escalation study will be reviewed and inform the design of a future Phase ll interventional trial prior to its initiation.

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. *CNGA3*-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 own experience from the existing clinical trials for ocular gene therapy, subsequent ocular gene therapy trials elsewhere (Maguire, *et al* 2008; Cideciyan, AV *et al* 2008 and 2013), the ongoing programme of work in ocular gene therapy trials investigating the safety and efficacy of *CNGB3* as a treatment for Achromatopsia, and pre-clinical data demonstrating improved outcome in both *CNGB3*- and *CNGA3*-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 are classified using the MHRA definition as Type C (Markedly higher than the risk of standard medical care). General risk management and the experience from all ongoing trials to date and will include, detailed review of all participants prior to administration of ATIMP, appropriate protocol design to identify potential short and long term risks appropriate time interval between ATIMP administration to successive participants and further limiting the risks to the child participants by first demonstrating an acceptable safety profile in both adults and children, with a similar vector, in a separate trial, MGT006.

. Details of specific risks and their management strategies are outlined below.

4.1.5.1 Risk of immune responses to AAV8-hG1.7p.coCNGA3

The main risk of inflammation will be during the early postoperative period after ATIMP administration and before vector capsids are degraded. This risk will be minimised by pre- and post-operative prophylactic treatment using topical and systemic corticosteroids. Any persistent intraocular inflammation will be managed by topical corticosteroid therapy and systemic corticosteroids where indicated. The participants will be closely followed up with a schedule of frequent assessments to identify and address any adverse events promptly.

In the first clinical trial of gene therapy (MGT003), intra-ocular delivery of an AAV2/2 vector was followed by transient intraocular inflammation in 3 of 12 participants. In our subsequent trials with the intraocular administration of AAV5 and AAV8 vectors has been well tolerated in the majority of participants. Similar episodes of intraocular inflammation involving the posterior segment in a minority of participants but all have responded to further administration of topical and systemic corticosteroids. Of the 2 SUSARs reported in the CNGB3 trial, the first, a panuveitis (MRN 2017-UK-000007), met the definition of a dose limiting event (DLE) (i.e. a reduction in visual acuity by greater than 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and responded favourably and promptly to treatment with additional corticosteroids. In the second SUSAR (MRN 2018-UK-000003), a 13 year old female participant was administered vector at the higher dose of 1.0 x 1012 vg/mL. An anterior / intermediate uveitis was reported, which did not itself constitute an SAE, but was associated with a temporary reduction in visual acuity by greater than 15 ETDRS and was, therefore, a dose limiting event that responded favourably and promptly to treatment with additional 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 8×10^{10} to 2×10^{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.

Pregnant or nursing (lactating) women will be excluded. Female patients of childbearing potential (e.g., are menstruating or could reach menarche during the study) should be counselled on the need for contraception should they be sexually active or, in the opinion of the Investigator, likely to be sexually active. Such subjects must agree to use an effective form of birth control (hormonal or double barrier method of birth control) for at least 12 months following ATIMP administration. Male patients who are sexually active must agree to use barrier and spermicide form of contraceptive during intercourse while taking the IMP and for at least 12 months after stopping treatment. Acceptable hormonal methods of contraception include combined pill, contraceptive implant, injection or patch, hormonal coil or progestogen-only pill.

Despite similar advice and protocol requirements across all trials, one pregnancy (MRN 2018-UK-000002) has been reported in our MGT004 trial, the longer-term follow-up trial for the MGT003 retinal dystrophy trial of gene therapy for RPE65 disease, with conception approximately 5 months following vector administration and normal delivery of a healthy infant at full-term. The most recent follow-up reports a positive outcome with both mother and infant being well.

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, including bleeding in the eye, infection and increased pressure inside the eye. 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. Reduction in foveal retinal thickness has been previously reported in a proportion of patients in both our first RPE65 trial and other RPE65 clinical trials, 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. However, in subsequent trials the use of a modified surgical technique that minimises the height of retinal detachment has resulted in no significant effect on foveal retinal thickness – most notably retinal thickness has been stable post-intervention in all 23 participants (11 adults and 12 children) in the CNGB3 trial.

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 this surgery specifically include persistence of the subretinal vector bleb, the development of retinal tears, elevated intraocular pressure and persistent postoperative intraocular inflammation. Persistently elevated intraocular pressure may result in glaucoma and vision loss; likewise, persistent inflammation may result in vision loss. Elevated intraocular pressure will be managed by topical therapy; with systemic therapy where indicated with specialist advice sought as required. Any potential risk to visual function will be minimised 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 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 immunocompromised status and increased risk of infections.Possible adverse effects of short-term systemic corticosteroid use include increases in blood pressure and blood sugar, weight gain, changes in mood or behaviour, increased risk of infections, increased intraocular pressure and cataracts. Local steroids used on or near the eye can cause increased intraocular pressure and cataracts. 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). Common and expected laboratory findings observed in the other ongoing studies utilising prophylactic corticosteroids have included but are not limited to: leucocytosis, neutrophilia, hyperglycaemia. If the latter should occur, then a referral to a diabetologist would occur. On occasion

mild transaminase changes have occurred but are mild and self-limiting. All the above have resolved with the tapering of the corticosteroids.

4.1.5.7 Risks of investigations performed during assessment and follow up

The majority of investigations are non-invasive routine clinical tests and presents no significant risk. Venepuncture causes temporary discomfort, occasionally bruising/swelling and rarely infection at the site of puncture. The participants will have all risks discussed during the consent process and are able to read them additionally in the Participant Information Sheet (PIS).

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 *CNGA3* 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 change in rod function has been described to date in the animal models (mouse and dog) used to demonstrate the potential of gene supplementation therapy in *CNGA3*-associated Achromatopsia.

There has also been no change in rod function in any of the 23 participants (11 adults and 9 children) in our current CNGB3 trial.

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 RPE65 clinical trial (MGT003). 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. However, in subsequent current trials the use of a modified surgical technique that minimises the height of retinal detachment has resulted in no significant effect on retinal thickness – most notably retinal thickness has been stable post-intervention in all 23 participants (11 adults and 9 children) in the CNGB3 trial.

Since the central macula comprises predominantly of cone photoreceptor cells that have no function in achromatopsia, therefore it is not expected that macular thinning to affect vision significantly in this trial. The participants intensive schedule of assessments (Table 5.6) has been designed to assess vision frequently.

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. The participants are made aware of this risk from the initial consenting process.

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. Emerging safety data from the ongoing *CNGB3* Achromatopsia trial provides further justification for the administration of vector to children in the dose escalation part of the current trial.

4.1.6 Explanation for Choice of Comparators

There is no currently approved treatment for Achromatopsia caused by mutations in *CNGA3.* The comparator will be the contralateral eye and supplementary data collected as part of a prospective, parallel natural history study of patients with Achromatopsia.

The totality of the data from paediatric subjects enrolled in the UK and adult subjects enrolled in the U.S. will be reviewed and inform the design of a future Phase ll interventional study.

4.2 Objectives

4.2.1 Primary Objective

The primary research objective is to assess the safety of an AAV2/8 vector for h*CNGA3* 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 that fails to resolve to within 15 letters of baseline in a 4-week period once prophylactic treatment commences
- 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 an AAV2/8 vector for h*CNGA3* 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 children with *CNGA3*-related Achromatopsia. Paediatric participants for the purposes of this protocol are participants aged up to and inclusive of 15 years of age. As part of the risk mitigation strategy for this protocol, ATIMP administration will first be administered to at least one older child participant (11- 15 years of age) from each cohort before proceeding to younger participants.

In this dose escalation study, up to 18 participants will be administered one of 3 different doses of the ATIMP in cohorts of 3 participants at a time in the first instance. Based on emerging safety data, the SDMC will make a recommendation on the dose to administer to the next cohort of participants. The SDMC may recommend additional participants at a given dose before making their recommendation on how to proceed to the next dose.

Paediatric cases for the purposes of this protocol are defined as participants aged up to and inclusive of 15 years.

In addition to the paediatric cohorts in the UK, an additional cohort of 2 adult subjects will be enrolled in the US. The adult cohort will be administered the highest dose studied from the paediatric cohorts based on when the first adult subject is identified and ready to be enrolled. The SDMC will review the data from all subjects (paediatric and adult) in this dose escalation study.

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. The totality of the data from paediatric subjects enrolled in the UK and adult subjects enrolled in the US will be reviewed and inform the design of a future Phase ll interventional study.

4.3.1.1 Separate longer term follow up study

In line with current CHMP and FDA guidance, the ATIMP safety is further assessed by a separate longer term follow up study of 60 months duration, if the participants / caregiver's consent and only once they have reached the 6-month timepoint in the current study. 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 February 2020 (Long Term Follow-up After Administration of Human Gene Therapy Products: Guidance for Industry) 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, 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 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 below dose-escalation criteria. 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, 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 SDMC chair will confirm additional doses 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 managed according to review of available and emerging data on the subjects administered ATIMP top date and the occurrence, if any, of DLE's or medically important events. An SDMC will review data from a minimum of 6 weeks of follow up from each cohort of participants (at least one older child, 11-15 years of age per cohort), before recommending the next dose to be assessed in a further cohort of participants or to additional participants at the same dose level.

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:

- A reduction in visual acuity by 15 ETDRS letters or more that fails to resolve to within 15 letters of baseline in a 4-week period once prophylactic treatment commences
- 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 SDMC prior to each dose escalation.

4.3.2.2 Dosing process

4.3.2.2.1 Cohort 1

ATIMP will first be administered at the lowest dose to at least one older paediatric (aged 11-15) participant only. This participant will be monitored for signs or evidence of visual and/or systemic toxicity for a period of 6 weeks and as per schedule of assessments (section 5.6). 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 additional paediatric participants. In the event of a DLE in the first cohort, a discussion will be held with the SDMC to agree a plan of action for the administration of ATIMP to further participants. The SDMC will review the data collected on this cohort up to 6 weeks following ATIMP administration to the last participant in the cohort.

4.3.2.2.2 Cohort 2

In the event that there is no DLE or other event considered clinically relevant to the progression of the study and dose escalation in any participant in cohort 1 the SDMC will provide a recommend to proceed administering ATIMP at the intermediate dose level. If dose escalation proceeds, at least a single older paediatric (aged 11-15) participant will be administered ATIMP. If there is no DLE or other event considered clinically relevant after a minimum of 6 weeks, ATIMP will continue to be administered at the same dose to 2 further participants. In the event of a DLE in the first participant in the cohort, a discussion will be held with the SDMC to agree a plan of action for administering the ATIMP to further participants. The SDMC will again review the data available on this next cohort of participants up to 6 weeks following ATIMP administration to the last participant in the cohort.

4.3.2.2.3 Cohort 3

In the event that there is no DLE (or clinically relevant event) in any participant in previous cohorts, the SDMC may recommend administering ATIMP at the highest dose level to a single older paediatric participant (aged 11-15 years) following review of all presented safety, toxicity and if relevant efficacy data. If there is no DLE or other event considered clinically relevant to the progression of the study after a minimum of 6 weeks, ATIMP will be administered at the same dose to 2 further participants. In the event of a DLE in the first participant in the cohort, a discussion will be held with the SDMC to agree a plan of action for administering the ATIMP to further participants, the age and the dose.

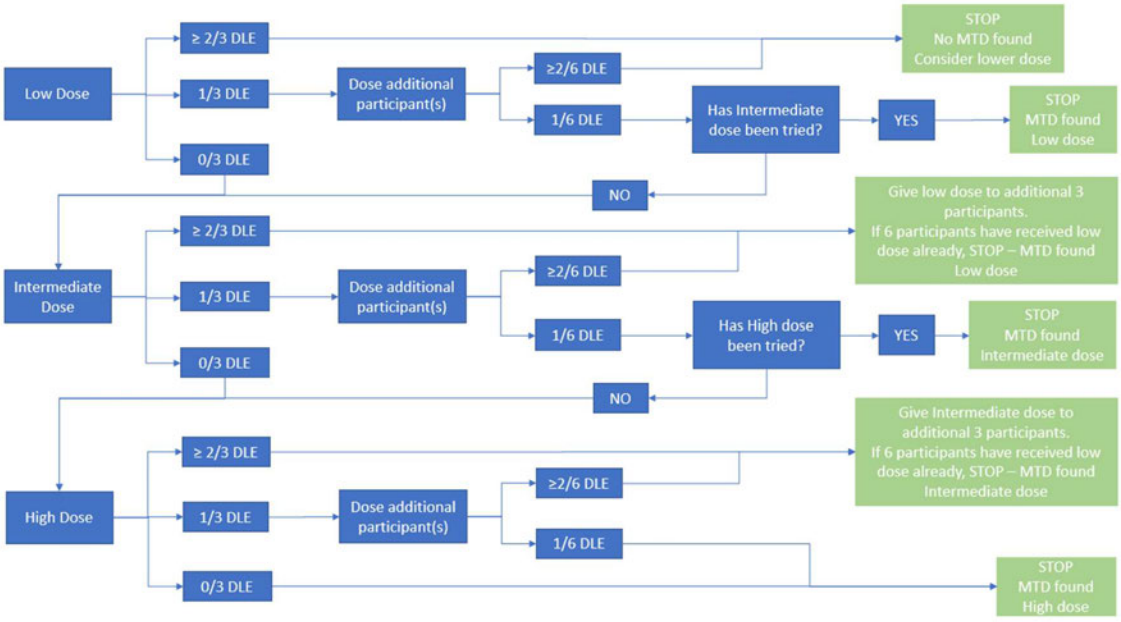
4.3.2.2.2.4 Adult Cohort-United States

In addition to the paediatric cohorts in the United Kingdom an additional cohort of 2 adult subjects, 18 years of age or older will be administered ATIMP at the highest dose studied from the paediatric cohorts based on when the first adult subject is identified and ready to be enrolled. The SDMC will also review the data from the adult cohort.

4.3.2.2.5 Additional considerations

In the event of a DLE in one of the participants at a given dose, the cohort may be expanded at the same dose level. The SDMC will review the safety data and recommend that additional participants may be treated at this dose. The SDMC may recommend that the same dose of ATIMP is administered to additional participants. The dose escalation will continue until SDMC are comfortable on review of the accumulating data, to recommend a maximum dose to be administered, 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 dose. In the event that 1 or 2 DLEs are seen at the first dose level, the SDMC may recommend administering a lower dose to that described in the protocol to a cohort of participants.

Table 1: Dose escalation table



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 multiple centres in the United Kingdom (UK) and 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 (*CNGA3)*, 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 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 (*CNGA3*) 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 require 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 3-15 years
2. Have Achromatopsia confirmed by a retinal specialist (PI)
3. Have homozygous or compound heterozygous missense or null mutations in *CNGA3* confirmed in an accredited laboratory. Segregation is highly desirable but not essential if parental samples are not available.
4. Have evidence of relative photoreceptor preservation at the macula assessed by OCT +/- AO. Participants with normal ISe or minimally disrupted ISe on OCT will be prioritised.
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 required 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 childbearing potential and sexually active, 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 and sexually active, 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 or surgically sterile (i.e. they have undergone a hysterectomy or bilateral oophorectomy)
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:
    - Uncontrolled hypertension defined as a systolic value ≥160mmHg or diastolic value ≥100mmHg.
    - Uncontrolled diabetes mellitus defined as an HbA1c ≥9% (75mmol/mol) at screening.
    - Any history of tuberculosis
    - Chronic kidney disease (defined as eGFR ≤60ml/min calculated using Cockroft Gault or MDRD equations.
    - Immunocompromised state (including long term immunosuppressant therapy).
    - Osteoporosis (defined as presence of 1 or more non-traumatic "fragility" fractures or proven BMD of 2.5SD less than anticipated as demonstrated on DEXA scan).
    - Active peptic ulcer disease or uncontrolled gastro-oesophageal reflux.
    - Severe affective disorder or past history of drug induced psychosis, and uncontrolled heart failure (NYHA class II-IV).
6. Use of high dose regular non-steroidal anti-inflammatory drugs at the time of screening

Will be excluded from participating in the study protocol:

- During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

    - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

        (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, e.g. fever, cough, dyspnea)

        AND

        (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

- NOTES on COVID-related exclusion:

1. If a patient is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.
3. Have an ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results
4. Have had intraocular surgery within 6 months of screening
5. 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. A training programme has been developed that involves any designated individuals being trained in person by Professor [redacted] (or an experienced surgeon who has been delegated this role by Prof [redacted]). 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' parents/guardians/person with legal responsibility (including legal authorities), and written assent must be obtained from children aged over 6, 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 9 months of the screening/baseline window of this study and prior to enrolment on this study may be used for baseline/screening if the subjects provide informed consent for the use of the prior obtained results.

5.3.1.6.1 Informed Consent Procedure

Written assent and informed consent as appropriate will be taken from each participant and parent/guardian 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.

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. The support of an independent counsellor or advisor will also be offered. 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 and their parents/carers will be provided with a further opportunity to ask questions and to sign the consent and assent forms. 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. Children under the age of 6 are not required to provide assent. A copy of the signed assent and 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) 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 9 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 CNGA3 mutations at an accredited laboratory prior to enrolment. If genetic screening has taken place as part of routine medical assessments the test may not be repeated, but the result will be reported in the CRF.

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. The study medical monitor should be consulted if the investigator is unsure or to discuss any other screening or eligibility issues.

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 (if no prior result available)
2. Medical history and concomitant medication (include 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. Spectral Domain Optical Coherence Tomography (SD-OCT)
8. 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 9 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 9 months of enrolment. If the ATIMP is not delivered within 9 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

AAV8-hG1.7p.coCNGA3 is an advanced therapy investigational medicinal product: specifically, a gene therapy product.

AAV2/8-hG1.7p.coCNGA3 is a gene transfer agent developed for the treatment of a form of Achromatopsia caused by defects in the gene encoding *CNGA3*. This is the alpha 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 *CNGA3* gene to the cone photoreceptors, results in stable, long term transgene expression and improves visual function significantly in both rodents and dogs with *CNGA3* gene defects.

AAV8-hG1.7p.coCNGA3 consists of a linear single strand of DNA packaged in a rAAV protein capsid of serotype 8. The AAV8-hG1.7p.coCNGA3 genome incorporates 290 nucleotides of the wild-type AAV2 ITR (Inverted Terminal Repeats) sequences that provide *in cis* the packaging signal, a cDNA encoding codon optimised human *CNGA3*, a human opsin locus control region and green opsin promoter (OPN1MW) 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 (AAV8-hG1.7p.coCNGA3) 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 MeiraGTx II Ltd., 92 Britannia Walk, London. N1 7NQ in accordance with current Good Manufacturing Practice for clinical trial materials. The product is released by an EU QP or as per country specific guidelines.

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 *CNGA3* 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 (rAAV8-hG1.7p.coCNGA3) to be administered to the subretinal space.

Delivery of vector suspension to the subretinal space will be performed by standard vitrectomy surgery. 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 commonly performed delivery of surgical dyes and antithrombotic agents in the management of rhegmatogenous retinal detachment and macular degeneration.

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 1 x 10^{12} vg/mL 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 (1 x 10^{12} vg/mL), 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 *CNGA3* transgene can be delivered to the cones effectively at 1 x 10^{12} vg/mL.

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

1. Cefuroxime can be administered subconjunctivally at 0.5ml normal saline, or 125mg in 1.0mL normal saline according to local practice or cefazolin or vancomycin antibiotic given at usual dose at end of surgery (standard dose as prophylaxis for post-operative infection)

2. Long acting steroid in the sub-tenon space following sclerotomy closure (see details in CNGA3 ATIMP Management Plan).

3. Betamethasone can be administered subconjunctivally at 2.mg- 5mg in 0.5mL, according to local practice, or dexamethasone can be administered subconjunctivally at 1.5mg-2.0mg in 0.5mL, according to local practice at end of surgery (standard dose as prophylaxis for post-operative inflammation)

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

5. Dexamethasone 0.1% (topical steroid) or topical prednisolone drops 1.0% should be administered 4 times daily for 4 weeks following ATIMP administration

4 and 5 above will be administered to minimise inflammation and protect against infection postoperatively.

6. Omeprazole:

- In children aged up to 15 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 15 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 to 15 weighing 20 kg (44 lb) or more: 20 mg taken once per day

Omeprazole will be administered as a gastro-protectant against corticosteroid therapy.

7. 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 9-month period to allow for day-to-day variation and test-retest variability for individual participants. However, it is acknowledged that a pragmatic balance will be achieved for what is appropriate for the different tests on an individual basis. Each set of baseline measurements may take up to 5 days to perform in total. Where it is not possible to obtain reliable data for any given baseline assessment, further protocol defined timepoints for those assessments will not be taken, unless required for evaluation of safety. In some instances, results for protocol specified baseline tests may be available as a part of routine clinical examination within 9 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 UK and US sites imaging with OCT, fundus autofluorescence and fundus photography will be reviewed by the site teams but also sent for independent analysis by the Reading Centre, Queens University, Belfast, Ireland, during the course of the trial. Adaptive optics images will be sent to the Medical College of Wisconsin, US, for reading. Octopus perimetry will be sent to the Oregon Health and Science University Casey Eye Institute, US, reading centre. Photoaversion videos will be sent to MeiraGTx and their research development partners. All images will be saved under pseudo-anonymised patient identifiers and surgical images will only be taken of the patient's eye to ensure that patients remain unidentified. Images and videos obtained during photoaversion testing may reveal some facial characteristics. To the extent possible, images and videos will be anonymised by removing any personally identifiable information from the imaging or video files.

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 a laboratory approved by the sponsor and their research development partners. 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
- At least one of static perimetry and / or full-field stimulus testing.
- Light-sensitivity (Photoaversion) testing

Tests that will be performed where possible unless lack of patient co-operation or equipment/ facilities are:

- Contrast sensitivity
- Reading assessment
- Colour vision testing
- Adaptive optics (AO) imaging
- QOL questionnaires

Further details of clinical assessments can be found in the Gene Therapy for Achromatopsia (*CNGA3*) 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, SD-OCT, and adaptive optics (AO) imaging. FAF imaging allows visualisation of the retinal pigment epithelium (RPE) by taking advantage of its intrinsic fluorescence derived from its lipofuscin content. SD-OCT

imaging enables measurement of retinal thickness and provides information about the integrity of the layers of the retina. AO imaging provides direct visualization of the photoreceptor mosaics *in vivo*.

(ii) Functional and Participant-Related Outcome Assessments.

Where possible the participant will complete an age appropriate Impact of Visual Impairment (IVI) vision-specific quality of life questionnaire, and EQ5D-5L questionnaire and EQ5D-Y questionnaire, or equivalent as appropriate. Reading ability including reading acuity, maximum reading rate, and critical print size will be assessed where possible.

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 perimetry and/or full field stimulus testing (FST) where possible.

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 anonymised video recordings and images will be stored alongside the trial database, with the sponsor and held by third party vendors.

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 as described in section 5.4.1.5.

Preoperative procedures and intraocular administration of ATIMP will be as described in the Gene Therapy for Achromatopsia (*CNGA3*) 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 involve 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) 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 (AAV8-hG1.7p.coCNGA3) 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/retinotomies. 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 with topical medication and systemic therapy where indicated, with specialist advice sought as required.

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 at a laboratory approved by the sponsor and their research development partners.

(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 5.4.2.1 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 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, 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 UCL Institute of Ophthalmology 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 National Genetics Reference Laboratory in the UK, or a CLIA-accredited molecular diagnostic laboratory in the US, for *CNGA3* mutation screening. Haematology and biochemistry samples and screen will be carried out at the Trust associated laboratories, or an accredited laboratory in the US.

Biochemistry and haematology parameters to be analysed are as per the table below:

Haematology	**Biochemistry**
Haemoglobin	Sodium
Haematocrit	Potassium
Erythrocytes	Chloride
Mean Corpuscular Volume	Bilirubin
Mean Corpuscular Haemoglobin	Alkaline Phosphatase
Platelet	Aspartate Aminotransferase

Leukocytes	Alanine Aminotransferase
Absolute Neutrophils	Lactate Dehydrogenase
Absolute Lymphocytes	Gamma Glutamyl Transferase
Absolute Neutrophils	Protein
Absolute Eosinophils	Albumin
Absolute Basophils	Calcium
	Magnesium
	Phosphate
	Urea
	Urate
	Creatinine
	Glucose

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 MeiraGTx II Ltd Manufacturing Facility (MeiraGTx MF), or other approved storage facility (details of storage will be specified in the ATIMP Management Plan).

The product, which is stable at ≤–70° 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 MeiraGTx MF. 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, 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 SDMC chair will confirm additional doses 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 appropriate dilution will be prepared in the operating theatre and this will be checked in 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 4.3.2.

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.

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 that fails to resolve to within 15 letters of baseline in a 4-week period once prophylactic treatment commences
- 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 baseline variation and are sustained for at least two consecutive assessments.
- Any improvement in retinal function from pre – intervention that is greater than the baseline variation and measurable by electrophysiology (pattern 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, or equivalent as appropriate.

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)		- 9 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[2]	●												
Pregnancy test	●				●								
Vital signs[3]	●	●				●		●	●	●			
Haematology[4]		●				●		●	●	●			
Biochemistry/glucose/liver and renal function[5]		●				●		●	●	●			
Serology		●								●		●	●
PCR						●				●			
QoL questionnaires (IVI and EQ5D-5L, or equivalent)		●											●
Visual acuity[6]	●	●	●	●		●	●	●	●	●	●	●	●
Colour vision assessments		●	●	●								●	●
Contrast sensitivity		●	●	●								●	●
Reading assessments		●	●	●								●	●
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)		- 9 months			Day 0	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 14D	± 14D
Fundus photography		●				●	●	●	●	●	●	●	●
Optical coherence tomography	●	●	●	●		●	●	●	●	●	●	●	●
Adaptive optics imaging		●	●										●
Fundus autofluorescence		●	●									●	●
Pattern Electroretinography[7]	●												●
Full field Electroretinography[7]	●												●
Photoaversion/ light sensitivity assessments (test ***and*** questionnaires)		●[8]	●[8]	●[8]								●[9]	●[9]

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

[2] If result is available from prior testing, no repeat test mandated. Result will be reported into the CRF.

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

[4] Hematology to include the following parameters: Haemoglobin, Haematocrit, Erythrocytes, Mean Corpuscular Volume, Mean Corpuscular Haemoglobin, Platelet, Leukocytes, Absolute Neutrophils, Absolute Lymphocytes, Absolute Neutrophils, Absolute Eosinophils, Absolute Basophils

[5] Biochemistry to include the following parameters: Sodium, Potassium, Chloride, Bilirubin, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine, Aminotransferase, Lactate Dehydrogenase, Gamma Glutamyl Transferase, Total Protein, Albumin, Calcium, Magnesium, Phosphate, Urea/BUN, Urate, Creatinine, Glucose

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

[7] ERG assessments may be performed under general anaesthesia if necessary.

[8] Photoaversion Questionnaire only to be completed at one baseline visit, "Photoaversion Device Questionnaire – Baseline" to be completed after every PA assessment

[9] "Photoaversion Device Questionnaire – after Surgery" to be used at week 12 and week 24 straight after Photoaversion assessments.

For management of visits delayed due to COVID_19 refer to appendix.

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 dose escalation 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 18 participants, as described in section 4.3.2.2. The limited number of participants is necessitated by the rare nature of the disease under investigation. The information obtained in this dose escalation study will help inform the design of a future Phase ll interventional study.

5.8 Recruitment and Retention

5.8.1 Recruitment

Most participants will be recruited through Moorfields Eye Hospital, UK, or the Kellogg Eye Centre, US, 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 18 participants in this dose escalation study.

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 AAV8-hG1.7p.coCNGA3 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).

5.10 Data Collection, Management and Analysis

5.10.1 Data collection, management and entry

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

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

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. Data Management 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 approved by the sponsor. 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 that fails to resolve to within 15 letters of baseline in a 4-week period once prophylactic treatment commences
- 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 18 participants. 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 baseline 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 baseline variation and measurable by electrophysiology (pattern 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.

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 Safety Data Monitoring Committee

To ensure the safety and efficacy and overall trial conduct, an SDMC will be established and take part in the data monitoring. The SDMC will consist of an independent consultant in pharmaceutical medicine who will be supported by the medical monitor, principal investigator and medical retina expert, and other independent uveitis or medical experts as required. The SDMC will make recommendations on the safety data prior to any dose changes.

Further details of the roles and responsibilities of the SDMC, including membership, decision making processes (and description of stopping rules and/or guidelines where applicable) are described in detail in the *CNGA3* Gene Therapy Trial for Achromatopsia SDMC 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 SDMC as agreed in the SDMC charter.

5.11.3 Data Monitoring for Harm

5.11.3.1 Safety reporting

Pharmacovigilance services will be delegated to an appropriately qualified and evaluated service provider.

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 *CNGA3* 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 childbearing age who are sexually active, 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.

Where appropriate, 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 the pharmacovigilance service provider 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 request the partner to contact us to ascertain the status of the pregnancy and the outcome. The pregnancy will be reported to PV Service Provider 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. The investigator may consult the study medical monitor for advice, but they will assume overall responsibility for the evaluation, assignment of clinical significance and reporting of adverse events. 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 the eCRF. These should be entered on to the database according to the timelines defined in the *CNGA3* Gene Therapy trial for Achromatopsia Data Management Plan to allow appropriate monitoring by the CMT. SAEs and SARs should be notified to PV Service Provider 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 PV Service Provider (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 5.0 (NIH, 2018).

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. The study medical monitor is available 24/7 to provide any advice as required

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 Pharmacovigilance

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 PV service provider 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.

PV service provider 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 PV service provider 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 PV service provider. 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
- Participant number
- 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.

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 PV service provider 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, participant 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 as per appropriate SOP.

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 PV Service Provider responsibilities

PV service provider will follow PV service provider Standard Operating Procedures and a study specific Safety Management Plan to ensure that case processing of events occurs within appropriate regulatory timeframes. PV service provider 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 *CNGA3* 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 Safety Data Monitoring Committee

The Safety Data Monitoring Committee (SDMC) 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 SDMC charter.

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 Clinical Trial Application 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

The parents of 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 parent is willing for their child to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the 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 the treatment of their child.

Children 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 (aged 11-15) 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 children 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 legally authorised representative will be asked to sign an updated consent form and assent will be sought as appropriate. 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 and when the child reaches the age of 16.

A copy of the approved consent and assent form are 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 and/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.

- Where data will be held/stored
- Rights that do not apply for research
- How and why data is being used

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 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/participant 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.

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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 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

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

6.11 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 and approved by the MeiraGTx UK II Ltd. 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. Where the presenter is not a MeiraGTx UK II Ltd. Representative, permission must be sought from MeiraGTx UK II Ltd.

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 Appendix: Guidance on Study Conduct during the COVID-19 Pandemic

This Appendix is intended for all ongoing studies at sites worldwide impacted by COVID-19. The measures outlined in this Appendix are temporary, while access to sites is restricted. As restrictions are lifted, the decision to revert back to the protocol in effect prior to the pandemic should be discussed and agreed with the sponsor.

It is recognised that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.
In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.
Scheduled visits that cannot be conducted in person at the study site will be performed remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfil any physical examination requirement.
If visits should be delayed past the visit window as per the schedule of events every effort should be made to see this patient as soon as it is deemed safe to do so whether this is due to the countries' Governing bodies restrictions being uplifted or under the advice of the CI of that site and patient's should not be made to wait until the next protocol visit.
Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the eCRF for protocol deviations and should be titled 'COVID-19 related'. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes (eg, delay or discontinuation in recruitment, site monitoring and audits) will be communicated to the sites and health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarised in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Each patient will be risk assessed on a case by case basis by the PI and his/her research team to decide the appropriate care for the patient.

Item no	Item	Management of Item
1	Missed assessments	Missed assessments will be captured in the EDC system as a deviation with the prefix COVID 19 RELATED.
2	Protocol Deviations	Any deviations to the study protocol due to COVID 19 pandemic will be captured in the EDC system will be entered with the prefix COVID 19 RELATED.
3	Baseline Assessments	Baseline assessments for those patients who have had surgery postponed due to COVID 19 - these baseline assessments will be valid up to 9 months except for Haematology, Biochemistry and Glucose which will need repeating.
4	Patients may be unable to attend study visit during visit window.	It is acknowledged that this is a global crisis and patients may be put at more risk attending hospital appointments due to route of travel into research facility. If appropriate the sponsor will offer expenses for taxi fares to avoid busy train or bus routes. If scheduled visits cannot be conducted within the visit window the site can schedule an additional visit at the earliest opportunity the patients is able to travel, ensuring no visits are completely missed unless authorised by the sponsor. If patients are unable to reach their research facility but are able to seek help at a local ophthalmologist for urgent concerns this is acceptable, and the sponsor will encourage patients to show any non-trial staff conducting assessments the contact details for the trial staff so that conversations can be had between the trial and non-trial medical staff
6	Patients visits conducted outside of visit window	Patients will be assessed individually by the sites on a case by case basis and phone interviews may be conducted by sites for all follow up visits up until at least 3 months post-surgery until on-site visits are possible. Patients undergoing telephone assessment will be asked to provide information on any adverse events or other safety concerns.
7	Patients self-quarantined or government implemented quarantine.	If patients and/or their caregiver are under quarantine and unable to leave home, their cases will be assessed by medical monitors and PI as to risk of delayed appointment. (e.g

		ongoing AEs, date of last appointment, less than 3 months since intervention).
8	Potential lack of reporting of symptoms due to delayed visits Delayed reporting of SAEs, SARs & SUSARs- Potential for events to not be reported within 24 hours of occurrence Delayed Participant reporting of Adverse Events	All participants are provided with emergency cards on enrolment to the study to enable 24-hour contact with study investigators. All events should be reported by an Investigator (as assigned on the delegation log) or another member of the site team, in the Investigators absence and where delegated, within 24 hours of the investigator/site being made aware. Sites have been advised how to still maintain timelines for reporting if impeded by pandemic restrictions.
9	Emergencies during the study and the provision of emergency contact arrangements:	If the participants facing difficulties in contacting the Trial Team in the event of emergencies, they have been provided with an alert card to inform other healthcare providers of their participation in the gene therapy trial. The Trial card includes the 24/7-hour contact number, patients trial code, trial number, brief details of the trial intervention and EudraCT number.
10	Patients may require NIMPs that they would have collected a scheduled study visit.	Site research staff will be in regular contact with their study patients and should they require NIMPs, the site pharmacy will be able to courier them to the patient and charge the cost to the sponsor.
11	Assessment results outside of window not true representation of protocol stated timepoints	Patient safety will be most important factor to consider. Patients will be invited as close to visit window as possible and deviations recorded where applicable.
12	Questionnaire responses could be incorrect due to expected visit vs actual visit attended.	Patient may confuse true answers if questionnaire asks for certain timepoints. Site research staff will explain questionnaire details before patient answers.
13	Clinician/s and site research staff unavailable due to contraction of virus	Site to ensure appropriate staff are available and documented on the delegation log to provide medical cover if the PI is unavailable.
14	Monitor may not be allowed on site or may be quarantined and unable to visit.	Monitors will be encouraged to attend site where possible, if unable will conduct remote monitoring as much as possible and arrange as many visits as is required to get back on track once site re-opens.

9 Protocol Amendments

Protocol Version and Date	Reason for Amendment
Protocol v1.0 16Nov2018	Initial version
Protocol v2.0 29Jan2019	Reduction of assessments based on analysis of CNGB3 MGT006 data to reduce assessment burden on participants and clinical sites and addition of optional MRI assessment.
Protocol v3.0	Update to contraception wording on request of MHRA
Protocol v4.0	Change of baseline/screening window prior to surgery from 6 months to 9 months. Addition of Photoaversion Device Questionnaires. Removal of MRI assessment
Protocol v5.0	Updated steroid & surgical risks, and local steroid use detailed. Guidance included on the management of patients during COVID-19 pandemic Further details added to exclusion criteria. Re-illustration of dose escalation table (no changes made)
Protocol v6.0	Removed dose expansion cohort (as this will now take part as a separate Phase II interventional study) Included details on additional adult cohort taking place in the US. Corrected inconsistencies

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