Long-Term Follow-Up Gene Therapy Study for Achromatopsia *CNGB3* and *CNGA3*

Long-term follow-up study of participants following open label, multi-centre, Phase I/II dose escalation trials of a recombinant adeno-associated virus vector (AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3) for gene therapy of adults and children with achromatopsia owing to defects in *CNGB3 or CNGA3*

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Authorisation: Sponsor Representative

Name	[redacted]
Role	Chief Medical Officer
Signature	[redacted]
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1 Administrative information

This document describes the longer-term Achromatopsia (CNGB3 and CNGA3) follow-up study, sponsored and co-ordinated by MeiraGTx UK II Ltd.

It provides information about procedures for entering participants into the study, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, study population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the study; replication of key aspects of study methods and conduct; and appraisal of the study'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 follow up 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 study.

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

1.1 Compliance

The study 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 UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable), and other local and national applicable regulations. The 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). Agreements that include detailed roles and responsibilities will be in place between participating sites and MeiraGTx UK II Ltd.

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 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 study, or
- The scientific value of the study.

1.2 Sponsor

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

1.3 Study Summary

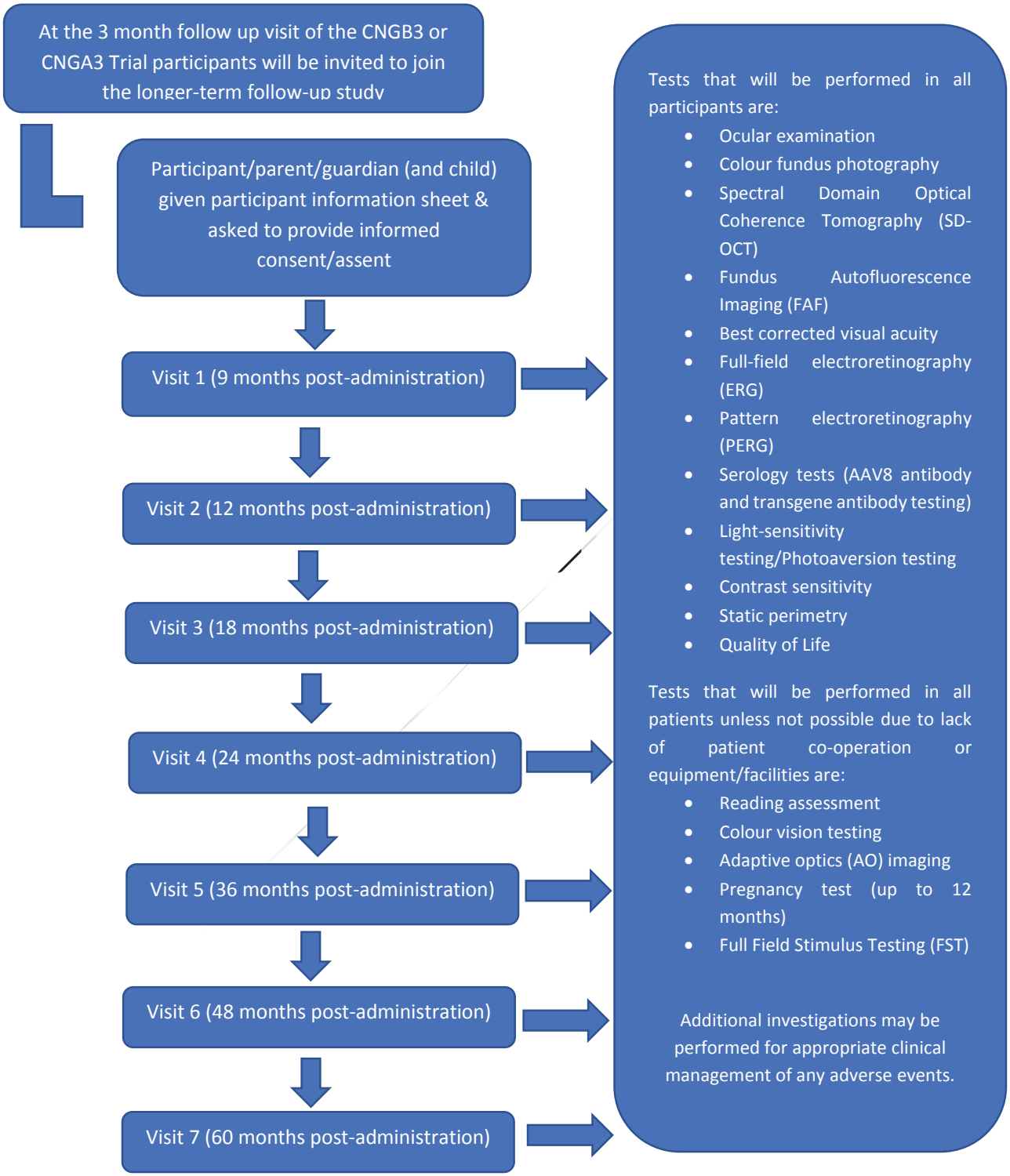
Primary Registry and study Identifying Number	EudraCT 2016-003856-59
Secondary Identifying Numbers	MeiraGTx UK II Ltd. registration number: MGT007
Sponsor	MeiraGTx UK II Ltd.
Contact for Public Queries	ocularinfo@meiragtx.com
Contact for Scientific Queries	[redacted] Professor of Retinal Studies UCL Institute of Ophthalmology 11-43 Bath Street London EC1V 9EL [redacted]
Public Title	Long-Term Follow-Up Study of Gene Therapy for Achromatopsia CNGB3 and CNGA3
Scientific Title	Long-term follow-up study of participants following open label, multi-centre, Phase I/II dose escalation trials of a recombinant adeno-associated virus vector (AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3) for gene therapy of adults and children with achromatopsia owing to defects in *CNGB3 or CNGA3*
Countries of Recruitment	United Kingdom, United States of America
Health Condition(s) or Problem(s) Studied	Achromatopsia associated with defects in *CNGB3 or CNGA3*
Key Inclusion and Exclusion Criteria	Inclusion in the study will be limited to individuals who: 1. Are able to give informed consent or assent, with or without the guidance of their parent(s)/guardian(s) where appropriate 2. Received AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3 by intraocular administration in the prior open-label, Phase I/II, dose escalation study (EudraCT 2016-002290-35 or EudraCT 2018-003431-29) 3. Are willing to adhere to the protocol and long-term follow-up Individuals will be excluded who: Are unwilling or unable to meet with the requirements of the study
Study Type	Long-term follow-up study of the safety and efficacy of participants following an open label, non-randomised, two-centre, dose escalation trial in adults and children with achromatopsia associated with defects in *CNGB3 or CNGA3*
Date of First Enrolment	October 2017
Target Sample Size	Up to 72 participants
Primary Outcome(s)	The primary outcome is longer term safety of subretinal administration of AAV8-hCARp.hCNGB3 (administered in the

	CNGB3 clinical trial) and AAV8-hG1.7p.coCNGA3 (administered in the *CNGA3* clinical trial) Safety will be assessed for 5 years after the intervention.
Key Secondary Outcomes	The secondary outcomes are measures of the longer-term efficacy of the original intervention: 1) Any improvement in visual function from baseline that is greater that the test-retest variation for that test and is sustained for at least two consecutive assessments. 2) Any improvement in retinal function from baseline that is measurable by electrophysiology and is greater than the test-retest variation. 3) Quality of life

1.4 Roles and responsibilities

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

2 Study Diagram



3 Abbreviations

AAV	Adeno-Associated Virus
Ad	Adenovirus
ADL	Activities of Daily Living
AE	Adverse Event
AF	Autofluorescence
AO	Adaptive Optics
AR	Adverse Reaction
ATIMP	Advanced Therapy Investigational Medicinal Product
ATMP	Advanced Therapy Medicinal Product
bps	Base pairs
BIOM	Binocular Indirect Ophthalmo Microscope
CA	Competent Authority
CCTV	Closed Circuit Television
cDNA	complementary Deoxyribonucleic Acid
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CI	Chief Investigator
CMT	Clinical Management Team
CNGA3	Cyclic Nucleotide-Gated cation channel Alpha-3
CNGB3	Cyclic Nucleotide-Gated cation channel Beta-3
CRF	Case Report Form
CRO	Contract Research Organisation
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
ETDRS	Early Treatment Diabetic Retinopathy Study
ERG	Electroretinography
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
FST	Full Field Stimulus Testing
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
H&E	haematoxylin and eosin
hCAR	Human Cone Arrestin
HIPAA	Health Insurance Portability and Accountability Act
HRA	Health Research Authority
HSE	Health and Safety Executive
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IRB	Institutional Review Board
ISCEV	International Society for Clinical Electrophysiology of Vision
KEC	Kellogg Eye Centre
LCA	Leber congenital amaurosis
Ltd	Limited (Company)

MHRA	Medicines and Healthcare Products Regulatory Agency
mL	Millilitre
ms	Millisecond
MTD	Maximum Tolerated Dose
mRNA	Messenger RNA
MP	Monitoring Plan
NHS	National Health Service
NIH	National Institutes of Health
NIMP	Non-Investigational Medicinal Product
OBA	Office of Biotechnology Activities
OCT	Optical Coherence Tomography
ONL	Outer nuclear layer
PCT	Polymerase Chain Reaction
PERG	Pattern Electroretinography
PHI	Protected Health Information
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
qds	quarter die sumendus (four times a day)
QOL	Quality of Life
qPCR	Quantitative Polymerase Chain Reaction
QP	Qualified Person
qPCR	Quantitative polymerase chain reaction
rAAV	Recombinant adeno associated virus
rAAV2/2	recombinant adeno-associated virus serotype 2
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
SmPC	Summary of Product Characteristics
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 Kingdome of Great Britain & Northern Ireland
USA	United States of America
vg	Viral Genomes
[redacted]	[redacted]
WT	Wild type

4 Introduction

4.1 Background

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

Achromatopsia resulting from mutations in *CNGB3 and CNGA3* has several characteristics that make it a good candidate disease to demonstrate proof-of-principle in a first-in-man trial of gene therapy for photoreceptor disease. Effective improvement in cone photoreceptor function, which is otherwise absent (or markedly reduced) in this condition, would provide a clear, rapid and reliable measure of outcome. In addition, achromatopsia is largely non-progressive and the extended survival of cones, despite their profound lack of function, presents a wide window of opportunity during which gene supplementation could lead to significant benefit in cone-mediated vision. Although younger individuals may benefit most from gene supplementation therapy by virtue of their greater visual plasticity, we anticipate that the intervention may offer benefit across a range of ages and we aim to define this range. For this reason, participants of various ages will be included; children (as defined by age in section 4.3) will be included once an acceptable safety profile has been established in adults.

4.2 Rationale

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 Photoaversion and nystagmus. The *CNGB3* gene encodes the beta subunit of the cone photoreceptor-specific cGMP-gated cation channel and the CNGA3 gene encodes the alpha subunit, both of which are critical for cellular responses to light. Absence of either the beta or the alpha subunit results in absent/extremely poor cone function and hence very poor daylight vision. Although loss of cone photoreceptor cells over time may occur in a limited number of patients, the rate of cell death appears to be very slow, resulting in retinas containing surviving but non-functioning cones. Improvement of cone function by provision of *CNGB3* or *CNGA3* (as appropriate) could provide a clear, rapid and reliable measure of outcome. Furthermore, the relatively non-progressive nature of achromatopsia, with extended survival of cone photoreceptors, means that the window of opportunity for effective intervention by gene supplementation may extend into adulthood.

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

The purpose of the CNGB3 and CNGA3 interventional trials and this longer term follow up study is to determine the safety and potential efficacy of the vector AAV8-hCARp.hCNGB3 and AAV8-hG1.7p.coCNGA3 respectively.

4.3 Assessment and Management of Risk

There is minimal risk to a participant by participating in this study as the assessments taking place are routine and generally non-invasive. The schedule of assessments in this study are designed to evaluate for longer term durability and safety associated with the subretinal administration of the antecedent gene therapy.

4.3.1 Risk of germline transmission

This risk was assumed in the antecedent interventional trial. The risk of inadvertent germline transmission is very small. In a number of studies using a variety of animal models involving various routes of administration, including intraocular injection, inadvertent germline transmission by rAAV vectors has not been detected. Similarly, we detected no vector genomes in semen 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 [redacted] were administered, considerably higher than the doses proposed for subretinal injection in this study. Whilst this indicates there may be some potential for inadvertent germline transmission following the systemic delivery of high doses of vector, the possibility of such an event following the microsurgical delivery of tiny amounts of vector to intraocular compartments is considered to be remote. Participants who are fertile and sexually active will be requested to use double-barrier contraception for at least 12 months following ATIMP administration.

4.3.2 Risk of investigations performed during assessment and follow up

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

4.4 Explanation for Choice of Comparators

This is a follow-up study to gene therapy studies MGT006 and MGT012, and is non-interventional. There is no comparator used in this study.

4.5 Objectives

4.5.1 Primary objective

The primary research objective is to assess the longer term safety of AAV8-hCARp.hCNGB3 for *CNGB3* gene replacement and AAV8-hG1.7p.coCNGA3 for *CNGA3* gene replacement in the retina administered to participants in the CNGB3 and CNGA3 trials, measured by the presence or absence of adverse events, the assessment of visual acuity, and loss of light perception.

4.5.2 Secondary objective

The secondary research objective is to explore the longer-term efficacy of AAV8-hCARp.hCNGB3 and AAV8-hG1.7p.coCNGA3 in improving visual and retinal function, and quality of life.

4.6 Study Design

Participants will be invited to provide consent for this longer-term follow-up study during the CNGB3 (MGT006) trial or CNGA3 (MGT012) trial. During this longer-term follow-up study participants will be assessed for safety for up to 60 months following AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3 administration in the MGT006 or MGT012 trial.

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 Food and Drug Administration (FDA) Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006) recommends a standard 15-year period of follow-up, it is also noted that a shorter period of follow up may be possible if the vector does not integrate and has no potential for latency and reactivation. The follow up study will be a non-intervention study designed to collect data on longer term safety and efficacy at the equivalent of 9, 12, 18, 24, 36, 48 and 60 months following ATIMP administration; as such, participants in both studies will be followed up more frequently than recommended in the guidance, as additional assessments following ATIMP administration are included in the initial studies of MGT006 and MGT012 (at Weeks 1, 2, 4 and 6) and in the long-term follow up study (at Months 9 and 18).

5 Methods

5.1 Site Selection

The study sponsor MeiraGTx UK II Ltd. has overall responsibility for site and investigator selection.

5.1.1 Study Setting

The study sites are academic hospitals and academic research centres selected for their ability to perform the intervention and assessments required of the CNGB3 and CNGA3 trials and this protocol. Participants will be recruited from centres participating in the CNGB3 trial MGT006 and CNGA3 trial MGT012.

5.1.2 Site/Investigator Eligibility Criteria

All investigative sites will be provided with a copy of this protocol and the ATIMP Investigator Brochures (IB).

To participate in this study, investigators and trial sites must have been participating sites in the *CNGB3* or CNGA3 trial as appropriate. They will be issued with the *CNGB3* and CNGA3 long-term follow-up study TMF documentation to use when applying for HRA or other local approval in the USA 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 clinical study protocol (confirming their specific roles and responsibilities relating to the study, and that their site is willing and able to comply with the requirements of the study). This includes confirmation of appropriate qualifications, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant study-related duties.

5.1.2.2 Resourcing at site

The investigator(s) should have an adequate number of qualified staff and facilities available for the foreseen duration of the study to enable them to conduct the study properly and safely.

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

5.2 Site approval and activation

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

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

The site must conduct the study 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 Eligibility Criteria

5.3.1 Participant selection

The eligibility criteria for this clinical study have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should be excluded to ensure that the study 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 study if they fulfil all the inclusion and none of the exclusion criteria as defined below.

5.3.2 Participant Inclusion Criteria

Inclusion in the study will be limited to individuals who meet the following criteria:

- Are able to give informed consent or assent, with or without the guidance of their parent/guardian where appropriate
- Were enrolled and treated in the prior open-label, Phase I/II, dose escalation study involving intraocular administration of AAV8-hCARp.hCNGB3 or AAV8-hG1.7p.coCNGA3
- Are willing to adhere to the protocol and long-term follow-up

5.3.3 Participant Exclusion Criteria

Individuals will be excluded if they are unwilling or unable to meet with the requirements of the study.

5.3.4 Enrolment into long term follow up study

Participants will be informed of the long term follow up study at the time of initial enrolment into the interventional CNGB3 or CNGA3 Phase I/II trials. Initial informed consent to participate in the long term follow up study will be initiated during the interventional trials. Each participant's consent to participate in the long term follow up study will be reconfirmed at the time of their first visit on this long term follow study (approximately 9 months after vector administration on the *CNGB3 or CNGA3* trial). Written informed consent to enter into the study must be obtained from participants, or parents/guardians/person with legal responsibility (including legal authorities) for children, after explanation of the aims, methods, benefits and potential hazards of the study and before any study-specific procedures are performed. Participants who fulfil the inclusion criteria and who provide informed consent will be enrolled in the study.

5.3.5 Informed consent procedure

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

The consent process will be managed by presenting information to potential participants in a form appropriate to their level of understanding. In the case of children, they and their legal guardian(s) will be offered the support of an independent counsellor or advisor. Potential participants will be provided with the relevant participant information sheets (or audio versions) and given time to consider their decision. They will be provided with the opportunity to ask questions and to sign the consent form. Children will be invited to give their verbal (and noted in their medical notes) or written assent to participation where this is age appropriate (i.e. children aged over 6 years). A copy of the signed Informed Consent form will be provided to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

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

Children who become of adult age (i.e. 16 in the UK, 18 in the US) during the study will be re-consented as adults at the time of the next visit.

5.4 Participation

5.4.1 Protocol Defined Clinical Schedule

5.4.1.1 Follow Up Assessments

Both safety and efficacy of the ATIMP will be evaluated at various time points, between 6 months and 5 years after ATIMP delivery, in this study. Evaluation will occur primarily by ocular assessments that will be read at independent reading centres in the UK and USA. Clinical assessments will be scheduled over a consecutive period of up to 3 days for each visit. The nature and schedule (Section 5.6, Assessment Schedule) of the follow up assessments is described below.

In addition, a serology test sample for evaluation of immune response will be drawn at each visit in this study (described as serology test in the Assessments Schedule table in Section 5.6).

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

Tests that will be performed in all participants are:

- Ocular examination
- Colour fundus photography
- Spectral Domain Optical Coherence Tomography (SD-OCT)
- Fundus Autofluorescence Imaging (FAF)
- Best corrected visual acuity
- Full-field electroretinography (ERG)
- Pattern electroretinography (PERG)
- Serology tests (AAV8 antibody and transgene antibody testing)
- Light-sensitivity testing/Photoaversion testing
- Contrast sensitivity
- Static perimetry
- Quality of Life

Tests that will be performed in all patients unless not possible due to lack of patient co-operation or equipment/facilities are:

- Reading assessment
- Colour vision testing
- Adaptive optics (AO) imaging
- Pregnancy test (up to 12 months)
- Full Field Stimulus Testing (FST)

Additional investigations may be performed for appropriate clinical management of any adverse events. Further details of clinical assessments can be found in the Gene Therapy for Achromatopsia (*CNGB3 and CNGA3*) study manuals. Images taken at all timepoints will be sent for independent reading and analysis at centres in both the UK and the US and to the sponsor and research

development partners. ERG assessments may be performed under general anaesthetic where considered appropriate.

5.4.1.1.1 Ocular examination and retinal imaging

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

Prolonged or recurrent intra-ocular inflammation will be managed conventionally by further topicaland/or systemic immunosuppression.

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

5.4.1.1.2 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.

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

The degree of light sensitivity (photoaversion) will be investigated in 2 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 or computerised (achromatic) spatial contrast sensitivity function tests.

Colour vision will be assessed comprehensively using plate tests and computerised tests probing colour discrimination along all 3 axes of colour and other testing methods may also be used as appropriate.

Retinal sensitivity will be determined using static perimetry and full field stimulus testing (FST) where available.

Full-field electroretinography (ERG), 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. ERG assessments may be performed under general anaesthesia if considered appropriate. ERG data will be analysed and interpreted by dedicated full-time Clinical Visual Electrophysiology Consultants at Moorfields Eye Hospital, UK, with extensive experience and who are directly involved in determining ISCEV standards.

5.4.1.1.3 Evaluation of immune responses

Up to 4 mL of blood will be sampled to measure immune response (AAV8 antibody and transgene antibody) at each visit (described as serology test in the Assessments Schedule table in Section 5.6).

Blood serum for immune response will be processed by a central laboratory. Antibody responses to AAV8 capsid proteins (for all subjects) and to CNGB3 protein (for CNGB3 subjects administered AAV8-hCARp.hCNGB3) or CNGA3 protein (for CNGA3 subjects administered AAV8-hG1.7p.coCNGA3) will be investigated by ELISA. Blood serum samples are prepared and stored under appropriate storage conditions (as described in the Sample Management Plan/Laboratory Manual) batched, and subject to periodic bioanalysis. Bioanalysis will be performed on collected samples in each subject until antibody levels comparable to baseline are seen in that subject, at which time no subsequent samples will be collected from the subject.

5.4.2 Concomitant Care

There are no restrictions around the concomitant use of other medications.

5.4.3 Protocol Discontinuation

5.4.3.1 Participant withdrawal

In consenting to the study, participants are consenting to study follow-up assessments and data collection.

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

Should a participant withdraw from the study, a withdrawal CRF documenting the reason for withdrawal will be completed.

5.4.3.2 Study Stopping Rules

The Chief Investigator and Sponsor retain the right to terminate the study. However, given the nature of the study assessing the safety and efficacy of the ATIMP administered in the CNGB3 or CNGA3 trial, it is not considered likely that this will occur.

5.5 Outcomes

5.5.1 Primary Outcomes

The primary study outcome is the long-term safety of the subretinal administration of the ATIMP.

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:

1) Any improvements in visual function from baseline that are greater than the test-retest variation and are sustained for at least two consecutive assessments.
2) Any improvement in retinal function from baseline that is greater than test-retest variation and measurable by electrophysiology (pattern ERG, or full-field ERG).

3) Quality of life will be measured by the Impact of Visual Impairment (IVI) questionnaire and the EQ5D-5L.

5.6 Assessment Schedule

Timings are since ATIMP administration.

	CNGB3/ CNGA3 M3[1]	M9	M12	M18	M24	M36	M48	M60
Visit no.		1	2	3	4	5	6	7
Informed consent	•	•						
Medical history		•	•	•	•	•	•	•
Pregnancy test		•	•					
Adverse event review		•	•	•	•	•	•	•
Concomitant medication review		•	•	•	•	•	•	•
Serology test (AAV8 antibody and Transgene antibody testing)		•	•	•	•	•	•	•
QoL questionnaires (IVI and EQ5D-5L)			•		•	•	•	•
Static perimetry		•	•	•	•	•	•	•
Visual acuity		•	•	•	•	•	•	•
Contrast sensitivity		•	•	•	•	•	•	•
Reading speed		•	•	•	•	•	•	•
Colour vision		•	•	•	•	•	•	•
Ocular examination		•	•	•	•	•	•	•
Fundus photography		•	•	•	•	•	•	•
Optical coherence tomography		•	•	•	•	•	•	•
Adaptive optics imaging		•	•	•	•	•	•	•
Fundus autofluorescence		•	•	•	•	•	•	•
Full field electroretinography[2]			•		•	•	•	•
Pattern electroretinography[2]			•		•	•	•	•
Photoaversion assessments[3]			•		•	•	•	•
Full Field Stimulus Testing[4]		•	•	•	•	•	•	•
Flexibility of schedule (±days)		21	21	60	60	60	60	60

[1] Initial consent for the long term follow up study will be obtained at the 3 or 6 month visit of the active CNGB3 or CNGA3 trial (or anytime thereafter).

[2] Electroretinography testing will be discontinued after M12 if responses remain undetectable

[3] To include testing with Photoaversion device and questionnaires

[4] Full Field Stimulus Testing will be discontinued after M12 if responses remain undetectable

5.6.1 Early Stopping of Follow-up

If a participant chooses to withdraw from the study, 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, this view must be respected. MeiraGTx UK II Ltd. should be informed of the withdrawal in writing using the appropriate study documentation. 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.

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 study.

5.6.3 Study Closure

The end of the study is considered the last follow-up visit of the last participant. For each participant, the study will terminate at the last scheduled visit 5 years following ATIMP administration. The MHRA and FDA will be notified of the end of the study within 90 days of its completion.

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

After the end of this study participants will return to their usual standard of care in their originating care teams.

5.7 Sample Size

This is a long term follow up study to establish safety and assess indicators of potential efficacy of the ATIMP administered in the CNGB3 trial and CNGA3 trial, therefore there is no formal sample size calculation.

The CNGB3 and CNGA3 trials will each include up to 36 participants (up to 18 in the dose escalation phase and at least a further 9 at the established maximum tolerated dose). We estimate that inclusion of up to 36 participants for each gene therapy will be sufficient to determine the safety and tolerability of the intervention. All participants enrolled in the CNGB3 MGT006 and the CNGA3 MGT012 trials will be invited to participate in this follow up study.

5.8 Recruitment and Retention

5.8.1 Recruitment

All participants will be recruited through participating sites from the CNGB3 MGT006 and CNGA3 MGT012 trial. Participants entering the CNGB3 and CNGA3 trials will be informed about this follow-up study during the consenting process.

5.8.2 Retention

Participants will be encouraged to remain in follow-up by regular contact as per the protocol.

5.9 Data Collection, Management and Analysis

5.9.1 Data, management and entry

[redacted] will be responsible for data management activities for the study.

Data will be captured in a fully validated, 21 CRF Part 11 compliant Electronic Data Capture (EDC) system provided by [redacted].

[redacted] will grant authorised site staff with access to the EDC system following system training and a successful competency assessment.

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

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

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

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

Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Prior and concomitant medication will be coded using the World Health Organization Drug (WHO)-Drug Dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system. Further coding details and data management processes will be described in a Data Management Plan (DMP).

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

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

5.9.2 Non-Adherence and Non-Retention

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

5.9.3 Statistical Methods

A formal Statistical Analysis Plan (SAP) will be written by the Sponsor for each gene defect programme. Analysis of the primary and secondary outcomes will be descriptive in nature. All outcomes for each product will be analysed and reported separately.

5.9.3.1 Statistical Methods – Primary Outcome Analysis

The primary outcome of each trial is safety of subretinal administration of the ATIMP.

The CNGB3 trial will include up to 36 participants (up to 18 in the dose escalation phase and a further 9 at the maximum tolerated dose) in whom safety will be assessed.

The CNGA3 trial will include up to 36 participants (up to 18 in the dose escalation phase and a further 9 at the maximum tolerated dose) in whom safety will be assessed.

5.9.3.2 Statistical Methods – Secondary Outcome Analysis

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

Efficacy will be indicated by:

1) Any improvement in visual function from baseline that is greater that the test-retest variation for that test and is sustained for at least 2 consecutive assessments.

2) Any improvement in retinal function from baseline that is greater than test-retest 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.

Any deviations from the original statistical plan will be described in the final report, as appropriate.

5.9.3.3 Statistical Methods – Health Economic Analysis

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

5.10 Data Monitoring

5.10.1 Independent Data Monitoring Committee

There is not an Independent Data Monitoring Committee for this trial.

5.10.2 Safety Data Monitoring Committee CNGA3

There is not a Safety Data Monitoring Committee for this trial.

5.10.3 Interim Analyses

No formal interim analysis is planned within the trial.

5.10.4 Data Monitoring for Harm

5.10.4.1 Safety reporting

The pharmacovigilance (PV) service provider will be responsible for pharmacovigilance services.

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

Table 1: 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.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
Unexpected Adverse Reaction	An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: (a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product, (b) In the case of any other investigational medicinal product, in the investigator's brochure relating to the study in question
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 CNGB3 or CNGA3 trial) that is DETECTED after administration. (This does not include pre-existing conditions recorded as such at baseline – as they are not detected after the administration of study drug.)
- continuous persistent disease or a symptom present at baseline that worsens following administration of study drug

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 treatment 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

5.10.4.2 Other Notifiable Events

Pregnancy is the only additional notifiable event that requires expedited reporting as detailed in Sections 5.10.4.3 and 5.10.4.4.

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

A pregnancy test is conducted for all females of childbearing age and the results are recorded in the medical notes before enrolling a volunteer to the CNGB3 or CNGA3 trial. Females with a positive pregnancy test at the time of planned ATIMP administration are to be excluded from the trial prior to administration of the ATIMP.

Participants are instructed to use barrier contraception for 12 months after ATIMP administration. However, it is difficult to 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 in the 12 months following ATIMP administration, the participant's GP will be notified 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 PV service provider on a pregnancy report form within 24 hours of the investigator becoming aware of the event, following the instructions on the pregnancy form. The participant will continue to be followed-up until outcome of the pregnancy. However, if the participant is unable or unwilling to participate further in the study, she will be encouraged to continue clinical monitoring visits to assess ocular health.

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

Participants are instructed to use double barrier contraception for 12 months after ATIMP administration. However, it is difficult to exclude entirely that the partner of a participant might become pregnant after administration of the ATIMP. In the unlikely event that the partner of a participant is found to be pregnant in the 12 months following ATIMP administration, the participant's GP will be notified that he is participating in a gene therapy trial and that, although the risks involved are minimal, there is a chance of gene transfer to the unborn child. With the participant's consent, we will contact the partner to ascertain the status of the pregnancy and the outcome. The pregnancy will be reported to The PV service provider on a pregnancy report form within 24 hours of the investigator becoming aware of the event, following the instructions on the pregnancy form.

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5.10.4.5 Investigator responsibilities relating to safety reporting

The Investigator will assume overall responsibility for evaluating and reporting adverse events. In urgent situations another member of the study team may report on their behalf, while making every effort to discuss the event with them. All non-serious AEs and ARs, whether expected or not, should be recorded in the participant's medical notes and reported in the toxicity (symptoms) section of the eCRF. These should be entered on to the database according to the timelines defined in the Data Management Plan to allow appropriate monitoring by the Clinical Management Team (CMT). SAEs and SARs should be notified to the PV service provider immediately after the investigator becomes aware of the event and 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 also be recorded in the hospital notes and the CRF. Adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate. All adverse events will be recorded until the end of the study, 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.

5.10.4.5.1 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 1. If the event is classified as 'serious' then an SAE form must be completed and emailed to the PV service provider (or delegated body) notified within 1 working day.

5.10.4.5.2 Severity or grading of Adverse Events

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

Table2: 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.

5.10.4.5.3 Causality

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

- The ATIMP administration surgery
- The ATIMP

The differentiated causality assessments will be captured in the study-specific CRF and SAE form using the definitions in Table 3.

Table 3: 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	Unrelated SAE

	time after administration of study drug). There is another reasonable explanation for the event (e.g., the participant's clinical condition or other concomitant treatment)	
Possibly related	There is some evidence to suggest a causal relationship (e.g., because the event occurs within a reasonable time after administration of study drug). 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

5.10.4.5.4 Expectedness

This is a long-term follow-up study to the prior interventional studies, and no intervention is given to participants in this study. Any expectedness assessment will be related to ATIMP and surgery given in the prior interventional study.

Table 4: Assessment of expectedness

Category	Definition
Expected	An adverse event that is classed in nature as serious and which is consistent with the information in the Investigator Brochure. In view of the very limited clinical experience with the ATIMP there are at present no events considered as expected for the ATIMP and surgery 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*.

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

The reference document to be used to assess expectedness of any SAE related to the ATIMP and/or administrative surgical procedure is the Reference Safety Information (RSI) section of the current Investigator Brochure (IB) for each programme respectively at the time the event started. The RSI section of the IB lists all the expected adverse reactions.

5.10.4.6 Notifications

5.10.4.6.1 Notifications by the Investigator to PV

All adverse events will be recorded in the hospital notes and the CRF.

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

Investigators should notify the PV service provider of any SAE occurring from ICF signature. Any events known to investigator that occur after the end of the study and that may be attributed to ATIMP

administration should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

The SAE CRF 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 study 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. 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 study number, patient number, year 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 entered as soon as it becomes available.

The SAE form must be scanned and sent by email to PV service provider as listed on the SAE form.

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 study follow-up (i.e., 5 years after delivery of ATIMP) if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the PV service provider as further information becomes available. Additional information and/or copies of test results etc may be provided separately. The participant's name must not be used on any correspondence and if the name does appear it must be blacked out and replaced with study identifiers on any test results. Any occurrence of a subjects'name must be reported to the clinical trial manager and investigated and remediated to prevent reoccurrence.

5.10.4.6.2 PV responsibilities

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

5.10.4.6.3 Reporting SUSARs in International Studies

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.

5.10.4.6.4 Annual Progress Reports

An annual progress report (APR) will be submitted by the sponsor to the UK 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.

5.10.5 Quality Assurance and Control

5.10.5.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for this study are based on the MeiraGTx UK II Ltd. Quality Management strategy that includes a formal Risk Assessment, and that

acknowledges the risks associated with the conduct of the study 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.

5.10.5.2 Clinical Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the Long-Term Follow-Up Gene Therapy Study for Achromatopsia owning to defects in CNGB3 and CNGA3 Monitoring Plan (MP) respectively. 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.

5.10.5.2.1 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 study related documentation as required. Participant consent for this will be obtained as part of the informed consent process for the study.

5.10.5.3 Study Oversight

Study oversight is intended to preserve the integrity of the study by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent and eligibility; adherence to 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 studies oversight is considered and described both overall and for each recruiting centre by exploring the study dataset or performing site visits as described in the study Monitoring Plan.

5.10.5.3.1 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.

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the study 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 study, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if the clinician feels it to be in the best interest of the participant. The reasons for doing so must be recorded. The participant remains free to change their mind at any time about the protocol 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 FDA in the USA).

This study does not involve the administration of an ATIMP. However, as the intention is to collect safety and efficacy data on participants administered an Advanced Therapy Investigational Medicinal Product in a previous trial (CNGB3 or CNGA3), which involves the application of monitoring procedures that are outside of the course of current practice for the management of achromatopsia, a CTA approval is required in the UK and an Investigational New Drug (IND) Application approval is required in the United States.

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

6.3 Other Approvals

A copy of the confirmation of local capacity and capability review (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).

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 study site.

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

6.5 Consent or Assent

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

Minors (as defined by local law) who are unable to consent for themselves will not be enrolled in the study without the consent of their parent(s) or legal guardian(s). Children or adolescents will be asked to assent or agree. A Participant Information and Assent sheet that describes the details of the study, study procedures, and risks in simplified form will be provided to minors who have the capacity to provide informed assent. Participation will 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, then he/she will be reconsented as an adult at the time of their next scheduled visit.

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

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

6.6 Confidentiality

All data will be handled in accordance with the UK General Data Protection Regulation 2018 (GPDR) , the Health Insurance Portability and Accountability Act of 1996 (HIPAA) or appropriate local data protection requirements.

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

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

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

Participant confidentiality will be held strictly in trust by the investigators, study 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 to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will use coded numbers only. Participants will not be identified in any publicly released reports of this trial.

Access to study 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 study-related monitoring, audits, REC/IRB review, and regulatory inspections by University or government entities. In these cases, the clinical 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 study participants. Study participants will be informed of this during the informed consent process.

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

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

6.7 Declaration of Interests

This study is funded by MeiraGTx UK II Ltd.

[redacted] declares ownership of minority shareholdings in MeiraGTx UK II Ltd. and receipt of payment 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 study. Participants may be able to claim compensation if they can prove that MeiraGTx UK II Ltd. has been negligent. However, as this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the study. MeiraGTx UK II Ltd. does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

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

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

6.9 Finance

This follow up study is fully funded by MeiraGTx UK II Ltd. It is not expected that any further external funding will be sought.

6.10 Archiving

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

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

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

Destruction of essential documents will require authorisation from the Sponsor.

6.11 Access to Data

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

Requests for access to study data will be considered, and approved in writing where appropriate, after formal application to MeiraGTx UK II Ltd.

6.12 Ancillary and Post-study Care

At the end of the follow up study, participants will resume usual standard of care within their primary care teams.

6.13 Publication Policy

All proposed scientific publications will be discussed with the Sponsor prior to publication. Study progress reports and significant findings may be presented at scientific forums/meetings and/or published during the course of the study. The results of the study will be disseminated regardless of the direction of effect.

7. Ancillary Studies

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

8 Protocol Amendments

Protocol Version and Date	Reason for Amendment
Protocol v1.0 dated 10 February 2017	Initial version
Protocol v2.0 dated 05 June 2019	Addition of Full Field Stimulus Testing at all visits in line with interventional protocol. Reduction in assessment burden in line with interventional protocols Addition of CNGA3 Achromatopsia trial
Protocol v3.0 dated 26 June 2019	Administrative error
Protocol v4.0 dated 07 Sep 2020	Vector names updated Assessment and Management of risks updated Evaluation of immune responses section added and Serology tests (AAV8 antibody and transgene antibody testing) added to assessments in protocol text and in assessments schedule. Independent Data Monitoring Committee and Safety Data Monitoring Committee information updated Administrative errors corrected
Protocol v5.0 dated 02Dec2021	Update to include patients and data from the MGT012 trial. Addition of Light-sensitivity testing/Photoaversion testing, Contrast sensitivity, Static perimetry and Quality of Life assessments to be performed in all participants New wording to the expectedness of AE/SAE.
Protocol v6.0 dated 03Dec2021	Administrative error

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