Gene Therapy for XLRP *RPGR*

An open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector (AAV2/5-hRKp.RPGR) for gene therapy of adults and children with X-linked Retinitis Pigmentosa owing to defects in Retinitis Pigmentosa GTPase Regulator (*RPGR)*

Version	11.0
Date	1st May 2020
Sponsor	MeiraGTx UK II Ltd
Sponsor registration #	MGT009
Trial registration	EudraCT 2016 003967 21
CTA #	45522/0004/001 0001
NRES #	218294

Authorisation: Co-ordinating Investigator

Name

Role

Signature

Date

Authorisation: Sponsor Representative

Name

Role

Signature

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1 Administrative information

This document describes the Gene Therapy trial for X-linked Retinitis Pigmentosa (XLRP) caused by mutations in the gene encoding Retinitis Pigmentosa GTPase Regulator (RPGR), sponsored and co-ordinated by MeiraGTx UK II Ltd.

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

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*. 2013[1]). The SPIRIT Statement Explanation and Elaboration document (Chan *et Al*. 2013[2]) can be referred to, or a member of MeiraGTx UK II Ltd. Clinical Operations team can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol and all applicable regulations. UK sites will comply with 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, and the UK Data Protection Act. US sites will comply with 21 CFR 312 in the Code of Federal Regulations, and the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (November 2013).

The participating sites will inform MeiraGTx UK II Ltd. as soon as they are aware of a possible serious breach of compliance, so that MeiraGTx UK II Ltd. can fulfil its requirement to report the breach if

necessary, within the relevant applicable timelines specified in each country in which the study is being conducted. For the purposes of reporting, a 'serious breach' is one that is likely to affect to a significant degree:

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

1.2 Sponsor

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

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	EudraCT 2016-003967-21
Secondary Identifying Numbers	MeiraGTx UK II Ltd. registration number: MGT009
Sponsor	MeiraGTx UK II Ltd.
Contact for Public Queries	ocularinfo@meiragtx.com
Contact for Scientific Queries	[redacted]
Public Title	*RPGR* XLRP trial
Scientific Title	An open label, multi-centre, Phase I/II dose escalation trial of a recombinant adeno-associated virus vector AAV2/5-hRKp.RPGR for gene therapy of adults and children with X-linked Retinitis Pigmentosa owing to defects in *RPGR*
Countries of Recruitment	United Kingdom, United States of America
Health Condition(s) or Problem(s) Studied	X-linked Retinitis Pigmentosa
Intervention(s)	Open label, dose-escalation • [redacted]
Key Inclusion and Exclusion Criteria	Key Inclusion Criteria: • Males aged 5 years or older (children will be included only once the maximal tolerated dose has been determined) • With Retinitis Pigmentosa caused by mutations in *RPGR* • Evidence of relative preservation of retinal structure at the macula • Able to undertake age-appropriate clinical assessments • Willing to give consent for the use of blood and blood components collected throughout the trial for the investigation of immune response to ATIMP Key Exclusion Criteria: • Intra-ocular surgery within 3 months of screening • Ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results. • Participated in another research study involving an investigational therapy for ocular disease within the last 6 months

	• Have any other condition that the 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
Study Type	Phase I/II, open-label, multi-centre, dose escalation in adults, followed by dose confirmation in children, followed by further randomised dose confirmation against a control arm in adults and children with XLRP owing to defects in *RPGR*
Date of First Enrolment	Q3 2017
Target Sample Size	Up to 71 participants
Primary Outcome(s)	The primary outcome is safety of subretinal administration of AAV2/5-hRKp.RPGR. Safety is defined as the absence of ATIMP-related: • Reduction in visual acuity by 15 ETDRS letters or more • Severe unresponsive inflammation • Infective endophthalmitis • Ocular malignancy • Grade III or above non-ocular SUSAR Safety will be assessed for 12 months after the intervention in this study, and a further 4 years in a separate follow on study (for deferred arm patients' safety will be assessed for 6 months after the intervention in this study and a further 4½ years in a separate follow on 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 12 months after the intervention: 1) Slowing or halting of progressive deterioration in retinal structure or visual function that is greater than the baseline variation for that test and is sustained for at least two consecutive assessments. Slowing or halting of progression over time may be facilitated by comparing identical structural and functional assessments acquired prior to intervention/injection to better determine rate of change over time in this slowly progressive disease. 2) 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. 3) Any improvement in retinal function from pre-intervention that is greater than baseline variation and measurable by electrophysiology (pattern ERG, multifocal ERG or full-field ERG). 4) Health- and vision-related quality of life measures (HRQoL, VRQoL).

1.4 Roles and responsibilities

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

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

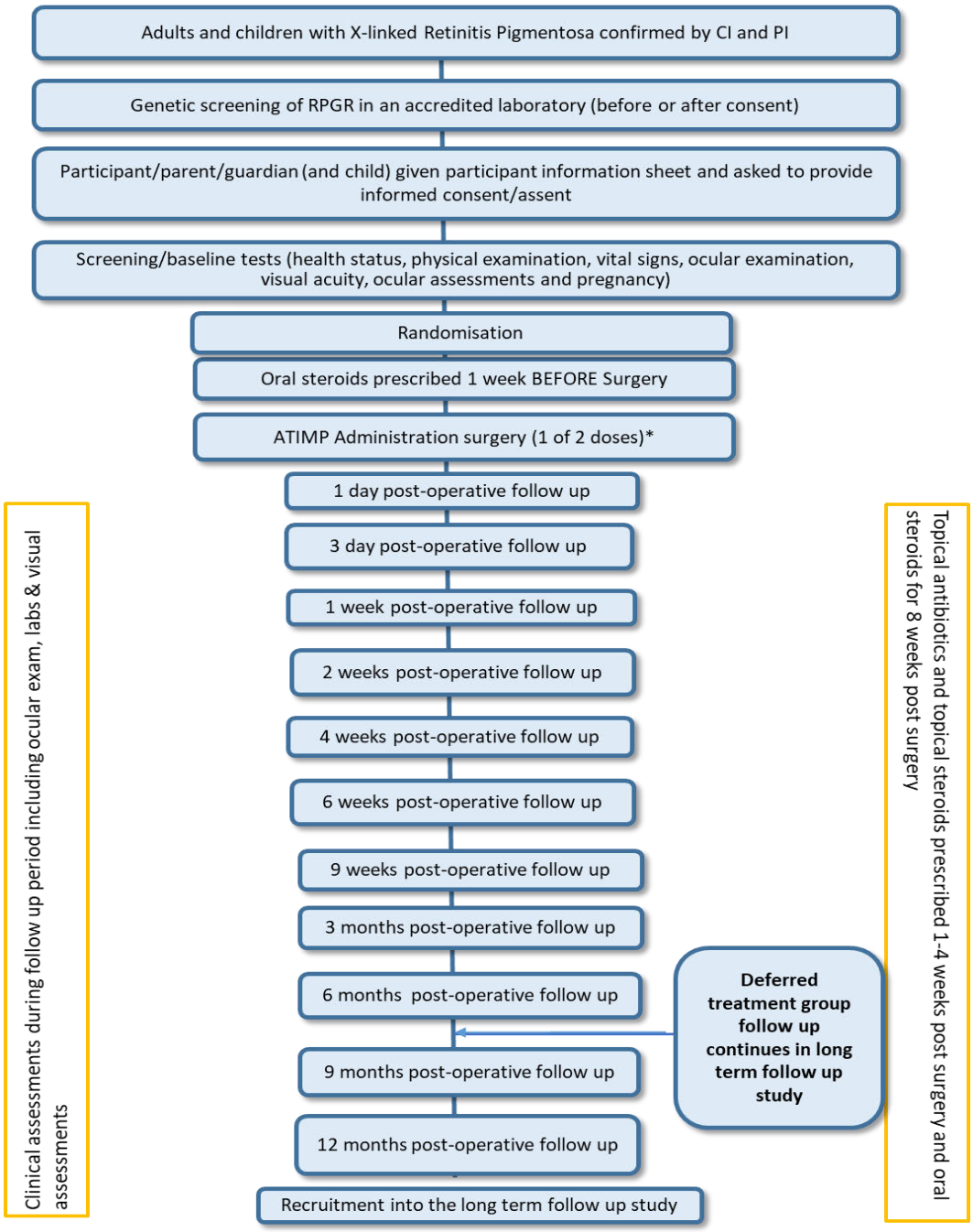
1.4.1 Protocol contributors

Name	Affiliation	Role
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1.4.2 Independent Data Monitoring Committee

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

2 Trial Diagram



* If randomised to the deferred treatment arm ATIMP administration will occur 6 months after screening, follow-up post administration will be for 6 months

3 Abbreviations

AAV	Adeno-Associated Virus
Ad	Adenovirus
AE	Adverse Event
AF	Autofluorescence
AO	Adaptive Optics
AR	Adverse Reaction
ATIMP	Advanced Therapy Investigational Medicinal Product
bps	Basepairs
BGL65p	*hRPE65* promoter fragment that is less efficient than the NA65p promoter
BNF	British National Formulary
CAI	Codon Adaptation Index
cDNA	complementary Deoxyribonucleic Acid
CGIC	Clinician Global Impression of Change
CI	Chief Investigator
CMT	Clinical Management Team
CMV	Cytomegalovirus
CNS	Central nervous system
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DAPI	4',6-diamidino-2-phenylindole
DLE	Dose-limiting event
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
EC	European Commission
eGFP	enhanced green fluorescent protein
ELISA	Enzyme-linked Immunosorbent Assay
ELISPOT	Enzyme-linked ImmunoSpot Assay
EMA	European Medicines Agency
EOSRDs	early-onset severe retinal dystrophies
EQ-5D-5L	EuroQOL Quality of Life 5 dimension 5 level
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FAF	Fundus Autofluorescence
FDA	(US) Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GFP	Green Fluorescent Protein
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GMSC	Genetic Modification Safety Committee
GTAC	Gene Therapy Advisory Committee
H&E	haematoxylin and eosin
hEBs	Human embryonic bodies
HEK293T	human embryonic kidney epithelial cell line
hRPE65	human retinal pigment epitheliumspecific protein 65 (all-*trans*-retinyl isomerase)
HSE	Health and Safety Executive
HTA	Human Tissue Authority
H2B	histone H2B
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier

IND	Investigational New Drug
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Trial Number
ITRs	Inverted terminal repeats
ITT	Intention to Treat
IV (or iv)	Intravenously
IVI	Impact of Visual Impairment
[redacted]	[redacted]
LCA	Leber congenital amaurosis
LCA2	Retinal dystrophy associated with defects in *RPE65*
LLQ	Low Luminance Questionnaire
LREC	Local Research Ethics Committee
MA	Marketing authorisation
Main REC	Main Research Ethics Committee
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
mRNA	Messenger RNA
NA65p	Optimised *hRPE65* promoter
NHS R&D	National Health Service Research & Development
NIH	National Institutes of Health
NIMP	Non-Investigational Medicinal Product
NRES	NHS National Research Ethics Service
NZW	New Zealand White
OBA	Office of Biotechnology Activities
OCT	Optical Coherence Tomography
ONL	Outer nuclear layer
ORF15	open reading frame 15
PCT	Polymerase Chain Reaction
PERG	Pattern Electroretinogram
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHI	Protected Health Information
PI	Principal Investigator
PIS	Participant Information Sheet

QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
qds	quarter die sumendus (four times a day)
QOL	Quality of Life
QMMP	Quality Management and Monitoring Plan
qPCR	Quantitative Polymerase Chain Reaction
QP	Qualified Person for release of CTIMP
qPCR	Quantitative polymerase chain reaction
rAAV	Recombinant adeno associated virus
rAAV2	recombinant adeno-associated virus serotype 2
R&D	Research and Development
REC	Research Ethics Committee
RG	Research grade
RK	Rhodopsin Kinase
RNA	Ribonucleic acid
RPE	Retinal Pigment Epithelium
RPE65	retinal pigment epitheliumspecific protein 65 (all-*trans*-retinyl isomerase)
RPGR	retinitis pigmentosa GTPase regulator
rt-PCR	reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	standard deviation
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Approval
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV40	Simian virus 40
TEI	Treatment Experience Interview

TMF	Trial Master File
ToR	Terms of Reference
tRNA	Transfer ribonucleic acid
UAR	Unexpected Adverse Reaction
[redacted]	[redacted]
XLRP	X-linked retinitis pigmentosa

USA	United States of America
vg	Viral Genomes
[redacted]	[redacted]
WT	Wild type

4 Introduction

4.1 Background and Rationale

4.1.1 Background

Retinitis pigmentosa (RP) is a group of inherited diseases of the retina, first described by Donders in 1857 (Donders, 1857). The condition is characterised by a progressive reduction in vision, initially manifest as night blindness which usually becomes apparent in childhood or early adulthood and is progressive throughout the subject's life-time. Owing to a number of X-linked forms, RP affects more men than women.

The prevalence of RP is estimated to be 1:3000 with 30-40% of cases inherited via an autosomal dominant route, 45-60% via an autosomal recessive route and 5-15% as an X linked (XL) trait. RP occurs most commonly in isolation (non-syndromic). Less frequently, RP may present as part of a syndrome such as Usher syndrome and Bardet-Biedl syndrome.

RP is characterised initially by night blindness (nyctalopia), progressive visual field constriction and finally decreased central vision in the advanced stage. The condition can manifest at any age from early childhood. Nyctalopia is commonly the first symptom, with difficulties in performing tasks in dark places or at night, such as navigating through dark rooms (e.g. cinemas), with a markedly impaired and delayed ability to adapt to dim ambient illumination. There is also progressive peripheral visual field loss with increasingly constricted peripheral vision. This results in 'tunnel vision' over time, which markedly restricts navigation / mobility and ability to undertake activities of daily living – with associated emotional, psychological and social impact. In the later stages continued retinal failure and degeneration results in central visual impairment and eventual blindness (Tee *et Al*. 2016).

Seventy to 80% percent of X-linked RP (XLRP) arises from pathogenic mutations in the retinitis pigmentosa GTPase regulator (*RPGR*) gene. *RPGR* associated XLRP (*RPGR* XLRP) is a particularly severe type of RP with an early onset of disease in childhood and relatively rapid progression.

For most forms of RP, including *RPGR* XLRP, the underlying mutations effect their pathological change through the dysfunction and subsequent loss of the photoreceptor cells, and thus the loss of light sensitivity.

4.1.2 Preclinical Data

Evidence for the medical plausibility of this gene therapy as a treatment for *RPGR* XLRP has been obtained from successful treatment in a mouse model of *RPGR* XLRP in which a slow progressive loss of photoreceptors is seen (Pawlyk*et al*., 2016). In this study, a vector carrying the construct that is intended for this clinical trial was subretinally injected into Rpgr-deficient mice, leading to a rescue of photoreceptor cell loss and a preservation of photoreceptor function. These investigations followed on from earlier work in which functional and morphological rescue of both rod and cone photoreceptor cells in Rpgr-deficient mice was demonstrated using an abbreviated murine *Rpgr ORF15* isoform as the transgene (Hong *et al.*, 2005). This earlier study supported the theory that a shortened human *RPGR ORF15* replacement gene, driven by a rhodopsin kinase (RK) promoter, is sufficient to rescue photoreceptor degeneration in *Rpgr*-null mice. This is important as the long purine-rich repetitive sequence of the ORF15 exon is unstable in many recombinant DNA manipulation procedures, presenting significant challenges to cloning a full-length cDNA from retinal RNA and, consequently, the ability to manufacture viral vector constructs packaging such a full length cDNA predictably and reproducibly to GMP.

The available data demonstrate that robust protein expression occurs with both of the abbreviated forms of RPGR.ORF15 studied (Pawlyk *et al*., 2016,Hong *et al.*, 2005) as evidenced by immunocytochemistry and western blotting data, with the latter showing that both forms of RPGR.ORF15 were expressed at levels that were similar to or slightly above that seen for the full length RPGR protein in a normal human retina. Both forms were seen exclusively in the photoreceptor cells but not in the retinal pigment epithelium (RPE) or the inner retina, indicating that the use of the RK promoter drives rod and cone photoreceptor cell specific expression at levels that are likely appropriate for clinical trials. Importantly, the data show that delivery of a human *RPGR.ORF15* gene in which around one-third of the purine-rich repetitive region is removed (*RPGR.ORF15-L*) results in RPGR protein that correctly localises to the connecting cilia of photoreceptors and corrects the disease phenotype (and therefore retains RGPR function *in vivo*). In contrast, use of the shorter isoform, *RPGR.ORF15-S* form, where most of the purine-rich region is removed, resulted in an inability of the protein to correctly localise to the connecting cilia and also failure to function correctly. In conclusion, the *RGPR.ORF15-L* gene, under the control of the RK promoter, results in expression of a functional RGPR protein and, subsequently, significant functional and morphological rescue of rods and cones in an animal model of *RPGR* XLRP.

Prior to the selection of AAV2/5 for the viral vector serotype, the Sponsor used human embryonic stem cell-derived cone photoreceptors (human ES cells differentiated into retinal cultures bearing human neuroepithelia containing human cones) to test the transduction efficiency of both AAV2/5 and AAV2/8 carrying GFP. In this experiment, human embryonic bodies (hEBs) were differentiated to retinal cultures and titre matched viruses were added between days 90-100 of culture. The transduced hEBs were collected after 2 weeks for immunohistochemistry and flow cytometry. The results showed that GFP+ cells were observed in all virally transduced human ESC-derived EBs and, analogous to their position in the human outer nuclear layer of the retina, these positive cells were mostly observed at the apical edge of the neuroepithelium.

To determine transduction efficiency of cone photoreceptors transduced by either the AAV2/5 or AAV2/8, vector-derived GFP co-localisation with red and green (L+M) opsins (MOPSIN) was assessed by immunofluorescence. Co-localisation of MOPSIN and GFP+ cells was observed in the neuroepithelium with both AAV viral vectors. Quantification of MOPSIN+/GFP+ cone cells by flow cytometry showed a non-significant difference in transduction efficacy between AAV2/5 and AAV2/8 serotypes.

Therefore, in the absence of any significant difference between the 2 serotypes, it is considered that the data generated with the AAV2/8 serotype can be extrapolated to AAV2/5. As it is the viral vector genome that is the central element that determines the efficacy of the treatment, the absence of a significant difference in transduction efficiency between the 2 serotypes suggested that the 2 serotypes were comparable and would have analogous potency in vivo. Based on this and commercial considerations the AAV2/5 serotype was selected to advance into clinical development.

4.1.3 Rationale

There is currently no licensed therapeutic treatment for *RPGR* XLRP. Among a variety of novel experimental strategies that are currently under investigation, gene therapy is considered the most promising. It is hypothesised that, in those subjects with RP associated with mutations in the *RPGR* gene, localised gene augmentation with a human RPGR-ORF15 variant will result in the production of a biochemically active RPGR-ORF15 protein and thereby facilitate functional and morphological rescue of both rod and cone photoreceptor cells and consequently improved vision.

4.1.4 Risk/Benefit

A gene therapy trial in human volunteers should not put the participants at disproportionate risk and for this reason should be restricted to individuals with serious disorders where effective treatments are not available. *RPGR* XLRP is chronically debilitating as evidenced by the severe impairment in visual function from early childhood and the consequent relatively rapid progressive loss of retinal cells, leading to inexorable blindness in the 3rd and 4th decades of life. The condition is currently untreatable, but there is a real possibility that gene therapy could offer a significant benefit in terms of markedly slowing/halting progressive retinal loss thereby preserving central vision, improved sight and quality of life (QOL). This is reinforced by our own experience from the 1st gene therapy trial for inherited retinal disease (Bainbridge, *et Al.* 2008), as well as subsequent ocular gene therapy trials by others (Maguire, *et al* 2008; Cideciyan, AV *et al* 2008 and 2013), and pre-clinical data demonstrating improved outcome in animal models of *RPGR* XLRP.

The safety of the proposed approach will be enhanced by restricting transgene expression to the target tissue by virtue of the photoreceptor-specific promoter, the inherent tropism of the AAV 2/5 vector, the direct administration to the sub-retinal delivery space and by restricting the intervention to one eye only in each participant.

4.1.5 Assessment and Management of Risk

The risk to participant safety in relation to AAV2/5-hRKp.RPGR, the ATIMP, is MHRA Type C (i.e. markedly higher than the risk of standard medical care). General risk management will include the detailed review of all participants, appropriate intervals between ATIMP administration to successive participants, the dose escalation plan, and limiting the risks to children by initially demonstrating an acceptable safety profile in adults. In addition, the schedule of participants' assessments has been designed to identify the short-term and the long-term risks. Details of specific risks and their management strategies are outlined below.

4.1.5.1 Risk of immune responses to AAV2/5-hRKp.RPGR

There is a risk that inflammation will occur following intra-ocular administration of rAAV in participants. The risk of inflammation is likely to be highest during the early postoperative period after ATIMP administration, before vector capsids are degraded. The risk of inflammation during this period will be minimised by pre, peri and post-operative prophylactic administration of topical and systemic

corticosteroids. In our 1st clinical trial of gene therapy, intra-ocular delivery of an AAV2/2 vector was followed by transient intraocular inflammation in 3 of 12 participants. In our subsequent trial of gene therapy, (including herein for low dose and intermediate dose AAV2/5-hRKp.RPGR) intraocular administration of an AAV2/5 has been well tolerated in the majority of participants to date. Some participants developed an episode of intraocular inflammation involving the posterior segment, which responded to further administration of systemic corticosteroids.

4.1.5.2 Risk of vector transmission to other organs

Biodistribution studies suggest that following subretinal injection of AAV, anterograde and trans-synaptic transport of small amounts of vector genome from the retina to central visual structures may occur (Stieger, *et al* 2008). This is considered most likely to result from off target transduction of retinal ganglion cells following reflux of vector suspension into the vitreous. Since only tiny amounts of vector are likely to reach the brain and a 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 human photoreceptor-specific promoter.

4.1.5.3 Risk 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 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 AAV2 to deliver factor IX in haemophilia B, can lead to vector sequences detectable in semen, though not sperm for a short period (Manno *et al* 2006). However, in this instance doses ranging from 8 x 10^{10} to 2 x 10^{12} vg/kg were administered, considerably higher than the doses proposed for subretinal injection in this study. Whilst this indicates there may be some potential for inadvertent germline transmission following the systemic delivery of high doses of vector, the possibility of such an event following the microsurgical delivery of tiny amounts of vector to intraocular compartments is considered to be remote. Participants who are fertile and sexually active will be requested to use barrier and spermicide contraception for at least 12 months following ATIMP administration.

4.1.5.5 Risk of surgical adverse effects

The risk of significant surgical adverse effects is similar to the standard surgical care for other common forms of vitreo-retinal disorders, 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. We have identified some reduction in outer retinal thickness and deterioration in acuity in 2 of the 12 participants in our previous clinical trial of gene therapy for LCA RPE65, believed to result from temporary retinal detachment which is a deliberate consequence of targeted administration of the vector suspension, but no other significant surgical adverse effects.

Delivery of ATIMP to the subretinal space will be performed by standard surgical vitrectomy. This will involve a 3-port pars plana vitrectomy followed by injection of ATIMP using a fine cannula through small retinotomies, resulting in a temporary retinal detachment. Previous gene therapy clinical trials have shown that the bleb of subretinal ATIMP suspension can be expected to resolve spontaneously over the course of the first 24 to 48 hours postoperatively as the fluid is absorbed by the underlying retinal pigment epithelium.

Potential complications of 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. We will minimise any risk to visual function by limiting ATIMP delivery to the area of retina most likely to benefit, and by leaving the contralateral eye untreated. Retinal detachment caused by persistent vector bleb or intraoperative retinal tear is expected to occur in fewer than 1 in 100 procedures and can be effectively managed in the majority by retinopexy, with or without intraocular tamponade. Persistent intraocular inflammation will be managed by topical corticosteroid therapy, with systemic corticosteroids where indicated. Elevated intraocular pressure will be managed by topical therapy; with systemic therapy where indicated with specialist advice sought as required. 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. 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 on day 1, day 3, day 7, week 2, week 4, week 6, and week 9, and blood glucose, renal function and liver function (at baseline and day 1, day 7, week 2, week 4, week 6 and week 9 after surgery).

4.1.5.7 Risk of investigations performed during assessment and follow up

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

4.1.5.8 Conclusion on the risk-benefit ratio

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

4.1.6 Explanation for Choice of Comparators

There is no currently approved treatment for XLRP caused by mutations in *RPGR* thus there are no comparators in this study. The contralateral fellow eye will be left untreated to minimise the risk to visual function and may also serve as a control given the relative inter-ocular symmetry of disease. There are no currently approved treatments for any forms of RP.

4.2 Objectives

4.2.1 Primary Objective

The primary research objective is to assess the safety of the ATIMP, AAV2/5-hRKp.RPGR, for *RGPR-ORF15* gene replacement in the retina of patients with *RPGR* XLRP.

Safety is defined as the absence of an ATIMP-related:

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

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

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

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

4.2.2 Secondary Objective

The secondary research objective is to determine whether AAV2/5-hRKp.RPGR for *RGPR-ORF15* gene replacement in the retina can slow/halt progressive deterioration in retinal structure or visual function, and improve retinal function, visual function and quality of life in patients with *RPGR* XLRP.

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 AAV2/5-hRKp.RPGR in participants with XLRP caused by mutations in *RPGR*.

In the dose escalation phase, up to 18 adult participants will be administered one of 3 different doses of the ATIMP in cohorts of 3 participants at a time. Based on toxicity data, the IDMC will make a recommendation on the dose to administer to the next cohort of 3 participants.

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

Once an acceptable safety profile has been established in adults, the IDMC will agree the maximum tolerated dose in adults before recommending administering up to this dose in the study. This maximum acceptable dose will be confirmed in paediatrics in the first instance.

Subsequent participants in the expansion phase will be randomised to one of 3 treatment groups (low dose administration: intermediate dose administration: deferred administration). Participants randomised to the deferred administration arm will also be randomised to receive either the low or intermediate dose. The eye selected for administration will also be randomised. All aspects of randomisation will be performed on completion of screening. Baseline assessments will be completed as soon as possible after randomisation and will be valid for 3 months[1]. See Section 5.9.1 for further details regarding randomisation. The deferred administration treatment group will perform baseline assessments as soon as possible after randomisation. At the end of baseline assessments, a day 0 will be applied and deferred administration follow up will be counted from this date. The deferred treatment group will be considered as a control group.

[1] For patients who surgery dates were postponed due to COVID 19 please refer to appendix 1

Safety and efficacy will be assessed for 12 months following the intervention by clinical examination and special investigations according to the schedule in section 5.6.

4.3.1 Separate longer term follow up study

Safety will be assessed in this study for 12 months following ATIMP administration (6 months for patients in the deferred arm). Participants will be invited to enrol in a separate subsequent follow-up study where they will be assessed for safety up to 60 months following ATIMP administration. The duration of long-term follow-up is therefore consistent with the recommendations of the current CHMP Guideline on Follow-up of Patients Administered with Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/60436/2007) of 22 October 2009, where it is stated that, for viral vectors without integration, latency or reactivation potential, a brief clinical history and sample testing should be performed pre-treatment, at 3, 6, 9 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 12 (deferred treatment control group only), 18, 24, 36, 48 and 60 months following ATIMP administration; as such, participants will be followed up more frequently than recommended in the CHMP guidance, as additional assessments following ATIMP administration are included in the initial study (at weeks 1, 2, 4, 6, 9 and month 9). 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 highly unlikely.

4.3.2 IMP Administration Review and Dose Escalation Criteria and Process

Up to 18 adult participants (as defined in section 5.3) will be administered one of 3 doses of ATIMP in a total maximal volume of 1mL, according to the dose-escalation criteria:

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

Once a maximal tolerated dose is established, up to 53 further participants aged 5 years or older will continue to be administered ATIMP up to the highest dose observed to be tolerated in adults. This includes up to 5 paediatric participants in the confirmation phase and up to 48 in the randomised phase.

4.3.2.1 Dose Escalation Criteria and Dose Limiting Events

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

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

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

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

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

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

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

4.3.2.2 Dosing Process

4.3.2.2.1 Cohort 1 [administration and immediate follow up is now complete in this cohort]

ATIMP will first be administered at the lowest dose to 1 adult participant only. This participant will be monitored for signs of toxicity for a period of 9 weeks. If there is no DLE as defined above after a minimum of 9 weeks, ATIMP will continue to be administered at the same dose to 2 further adult participants. In the event of a DLE in the 1st adult in the cohort, the cohort will be expanded to a possible total of 6 participants. A discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further adults. The IDMC will review the data collected on this cohort up to 9 weeks following ATIMP administration to the 3rd participant.

4.3.2.2.2 Cohort 2 [administration and immediate follow up is now complete in this cohort]

In the event that there is no DLE in any participant, the IDMC will recommend administering ATIMP at the intermediate dose level to a single adult participant. If there is no DLE after a minimum of 4 weeks, ATIMP will continue to be administered at the same dose to 2 further adult participants. In the event of a DLE in the 1st adult in the cohort, an additional 3 participants will may be treated at this dose level. A discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further adults. The IDMC will again review the data available on this next cohort of adult participants up to 9 weeks following ATIMP administration to the 3rd participant.

4.3.2.2.3 Cohort 3 [administration and immediate follow up is now complete in this cohort]

If the IDMC recommends it is safe to dose escalate to the highest dose, then ATIMP will be administered at the highest dose level to a single adult participant. If there is no DLE after a minimum of 4 weeks, ATIMP will be administered at the same dose to 2 further adult participants. In the event of a DLE in one of the 3 participants at this dose, the cohort may be expanded to up to 3 additional participants at this dose level. A discussion will be held with the IDMC to agree a plan of action for administering the ATIMP to further adults.

4.3.2.2.4 Additional considerations

In the event of a DLE in 1 of the 3 participants at a given dose, the cohort may be expanded and additional participants treated at the dose level. The IDMC will review the safety data and confirm that additional participants may be treated at this dose. The dose escalation will continue until:

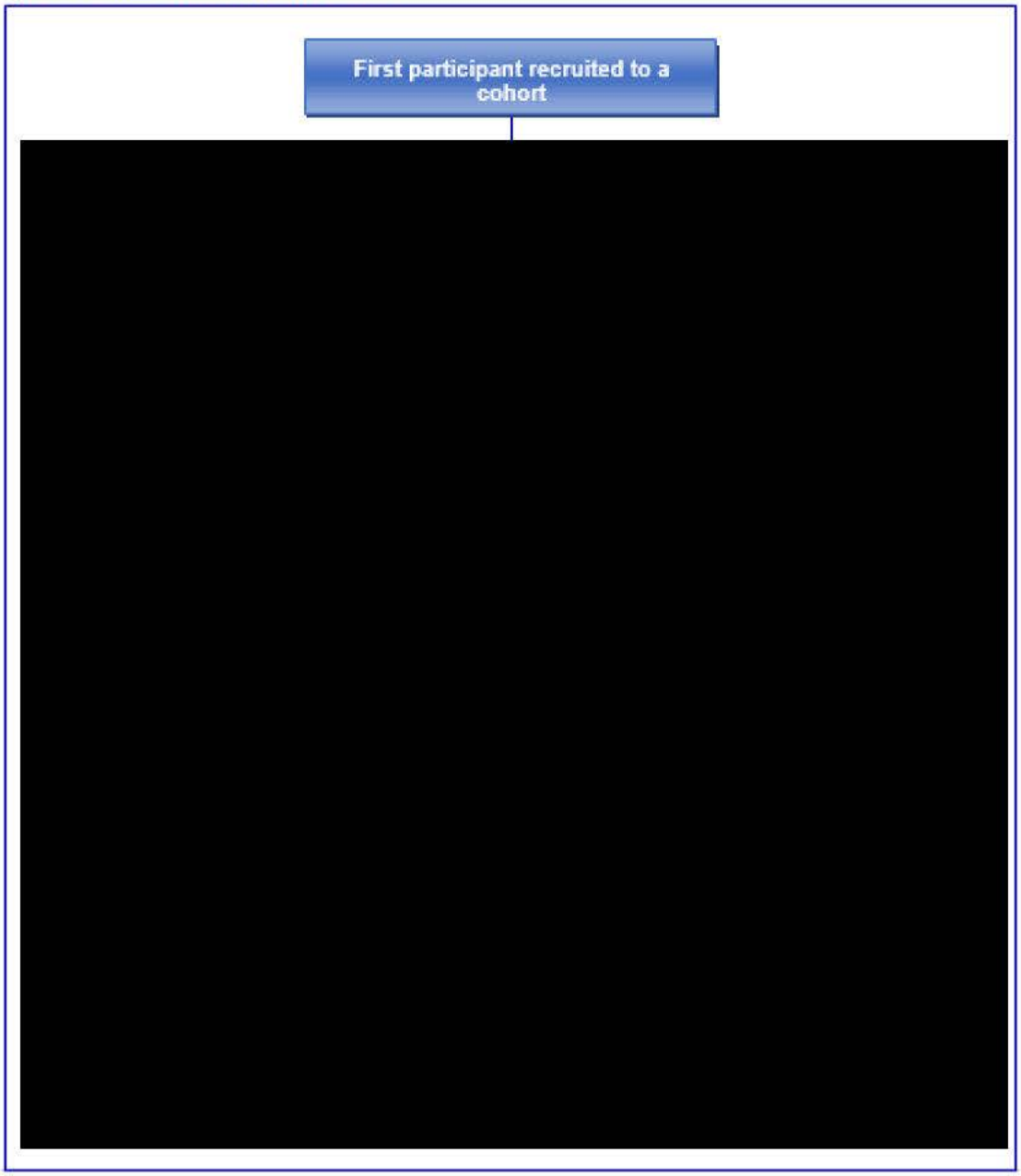
- On review of the accumulating data the IDMC recommend a maximum dose to be administered in the expansion phase;
- 3 participants have been administered the highest dose without any DLEs; or
- until at least 2 participants among a cohort of 3 to 6 participants experience DLEs (i.e., ≥33% of patients with a DLE at that dose level), in which case the recommended maximum anticipated therapeutic dose will be the level below.

In the event that 1 or 2 DLEs are seen at the 1st dose level, the IDMC may recommend administering a lower dose to that described in the protocol to a cohort of participants.

Table 1: Dose escalation and confirmation table

Number of DLEs			
Low dose			
Participants 1-3	**Participants 4-6**	**Action**	**Details**
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Intermediate dose			
Participants 1-3	**Participants 4-6**	**Action**	**Details**
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
High dose			
Participants 1-3	**Participants >3**	**Action**	**Details**
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Figure 1: Dose escalation Flow chart



4.3.2.2.5 Confirmatory Safety Phase

The adult dose escalation component of the study is complete at the time of protocol amendment v9.0. Review of the data collected to date with the IDMC led to a decision not to pursue the higher dose level and to commence administration for confirmation in paediatrics at the intermediate dose level. Children are defined as those aged 15 and under in the UK, and 17 and under in the US. These participants in the paediatric confirmation phase are administered the intermediate dose [redacted] which has

been shown to be well tolerated in adults. Having identified children who may be willing to participate in the study, the CI will prioritise ATIMP administration to older candidates in the 1st instance. The 1st child administered ATIMP will be monitored for safety for a period of 4 weeks. If there is no adverse event consistent with the above definition of a DLE after 4 weeks, ATIMP will be administered to further children.

In order to fully explore dose levels and make optimal use of the expansion phase of the study, a treatment group randomisation will subsequently occur to either low or intermediate dose; to achieve up to 32 participants receiving intervention at baseline, and up to 16 further participants receiving deferred intervention at 6 months following baseline (control group). The expansion phase will include up to 48 participants in total, who may be adults or children.

Therefore, participants will be randomised to 1 of 3 arms in a 1:1:1 ratio (immediate low dose administration (n= up to 16): immediate intermediate dose administration (n= up to 16): deferred administration (n= up to 16)). Participants randomised to the deferred administration group will be further randomised to receive the low or intermediate dose in a 1:1 ratio (deferred low dose administration (n= up to 8): deferred intermediate dose administration (n= up to 8)). The eye selected for administration will also be randomised. All aspects of randomisation will occur on completion of screening. (Figure 2: Randomisation Timeline). Baseline assessments will be completed as soon as possible after randomisation and will be valid for 3 months[2]. In the deferred treatment group, a day 0 will be applied at the end of baseline assessments and deferred treatment follow up will be calculated from this date. The three treatment groups of the randomised expansion phase will be stratified by age at date of informed consent (<25 years, ≥25 years) to balance for disease severity between treatment groups with age used as a surrogate for severity.

[2] For patients who surgery dates were postponed due to COVID 19 please refer to appendix 1

Figure 2: Randomisation Timeline

Time (months)	
0	Participant completes screening Randomisation 1: Eye selected for administration Randomisation 2: Treatment Group • Low • Intermediate • Deferred (Control Group) Randomisation 3: Dose selected for administration to Deferred (Control Group) • Low • Intermediate
6 months after completion of baseline assessments in deferred treatment group	Control group administered low or intermediate dose Interim analysis performed 3 and 6 months post- surgery of the last participant in the low or intermediate treatment arm
12	Follow-up complete

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 is anticipated to be collected from centres in the United Kingdom and the United States of America.

5.1.2 Site/Investigator Eligibility Criteria

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

To participate in the *RPGR* XLRP trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the Clinical Management Team (CMT) and that are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are available to recruit participants, enter data and collect samples
- Suitably trained and certified staff are available to undertake clinical assessments

- The site has access to all specialised equipment/devices needed for clinical assessments
- The site is able to archive traceability data for a minimum 30 years post expiry date of the ATIMP
- The site has a pharmacy that can store, prepare and dispense ATIMP appropriately
- The site can store, prepare 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 *RPGR* XLRP 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, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

5.1.2.2 Resourcing at site

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

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

5.2 Site approval and activation

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

On receipt of the signed Clinical Trial Agreement and Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any participants until a letter of formal 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 Research Ethics Committee (REC) in the UK and local Institutional Review Board (IRB) in the US. The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the Clinical Operations team at MeiraGTx UK II Ltd.

5.3 Participants

5.3.1 Eligibility Criteria

5.3.1.1 Participant selection

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria will 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 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 meet the following criteria:

1. Are males aged 5 years or older
2. Have X-linked retinitis pigmentosa confirmed by a retinal specialist (CI or PI)
3. Have relatively symmetrical retinal disease - both structurally and functionally defined as < 15 letters [Best Corrected Visual Acuity (BCVA)] difference between eyes
4. Have a predicted disease-causing missense or null mutation in *RPGR* confirmed in an accredited laboratory
5. Evidence of relative preservation of retinal structure at the macula

6. Evidence of impaired navigation in dim illumination on Mobility assessment in **both** eyes monocularly; defined by either an inability to complete the visual mobility maze at the 1 lux level, or the time taken to complete the maze at either 1 or 4 lux being greater or equal to 12 seconds.
7. Are able to give informed consent or assent, with the guidance of their parent/guardian where appropriate: children aged 5-6 years will not be asked to provide assent
8. Are able to undertake age appropriate clinical assessments at the trial sites as specified in the protocol
9. Are willing to use barrier and spermicide form of contraception or will be sexually abstinent (when this is in line with the participant's preferred and usual lifestyle) for at least 12 months following ATIMP administration
10. Are willing to give consent for the use of blood and blood components collected through the trial for the investigation of immune responses to the ATIMP

5.3.1.3 Participant Exclusion Criteria

Individuals will be excluded if they meet any of the following criteria:

1. Have a known allergy to any of the non-investigational drugs to be used in the trial as defined in Section 5.4.1.
2. Have participated in another research study involving an investigational medicinal therapy for ocular disease within the last 6 months.
3. 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.
    - Uncontrolled heart failure (NYHA class II-IV).
    - 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

4. Use of high dose regular non-steroidal anti-inflammatory drugs at the time of screening.
5. Have an ocular or systemic disorder that may preclude subretinal surgery and/or interfere with interpretation of the study results.
6. Have had intraocular surgery within 3 months of screening.
7. Have recently (within 4 weeks of last dose of concomitant immunosuppressive therapy) received a live vaccine.
8. Have a condition that requires glucocorticoid replacement therapy, such as in endocrine diseases, if this would interfere with the immunosuppressive regime.
9. Have known chronic hepatitis B infection as indicated by detectable surface antigen. Entry with negative surface antigens but positive hepatitis core antibody will be allowed; however additional monitoring throughout the trial may be required.
10. 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 the interventions.

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

5.3.1.5 Co-enrolment Guidance

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

5.3.1.6 Screening Procedures

Written informed consent to enter the trial must be obtained from participants, or parents/guardians/person with legal responsibility (including legal authorities) for children, after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific

procedures are performed or any blood is taken for the trial. However, results of any procedures that were performed as part of the usual standard of care within the screening/baseline window of MGT009 and prior to enrolment on this study may be used for baseline/screening if the subjects provided informed consent for the use of the prior obtained results. Any participant entering the study with a known genetic confirmation of disease-causing missense or null mutation in *RPGR* from an accredited laboratory does not need to have this assessment repeated during screening. In addition, data obtained previously from subjects enrolled on the MGT011 RPGR Natural History Study may be used for screening and/or baseline data if testing was performed within the screening/baseline window of this trial and the subjects have provided informed consent for the use of the prior obtained results.

5.3.1.6.1 Informed consent procedure

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

The consent process will be managed during interactions on at least 2 occasions. The 1st occasion will involve information being presented to potential participants in a form appropriate to their level of understanding. In the case of children, they and their legal guardian(s) will be offered the support of a family support counsellor (in the UK) or genetic counsellor (in the US). Potential participants will be provided with the relevant participant information sheets (or audio versions) and given time (a minimum of 24 hours) to consider their decision.

At a subsequent occasion, potential participants will be provided with a further opportunity to ask questions and to sign the consent form. Children will be invited to give their verbal (and noted in their medical notes) or written assent to participation where this is age appropriate (i.e. children aged over 6 years). 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. Reconsent may be conducted by telephone if appropriate or in person at the participant's next scheduled study visit. If reconsent is taken by telephone, the designated site staff taking reconsent must explain the need for reconsent and give the participant an opportunity to ask questions. The informed consent process and information provided to the participant by telephone must be documented in the patient notes including details of the information provided, by whom, and date of the interaction.

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. Younger children who become 11 years of age during the study will be given the information sheet and assent form for older children to assent at the time of their next study visit. Likewise, younger children (aged 6 or less) who become old enough to provide assent during the course of the study will be asked to assent at their next visit.

5.3.1.6.2 Screening Period

Screening procedures will only take place 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 or participation in the MGT011 RPGR natural history study, and the subject has consented to allow the use of those test results, then those screening tests will not need to be repeated.

Participants will undergo genetic screening for *RPGR* mutations at an accredited laboratory prior to enrolment. Any participant entering the study with a known genetic confirmation from an accredited laboratory does not need to have this assessment repeated during screening.

Participants will be screened to ensure there are no contra-indications for transient immune suppression, in particular: uncontrolled hypertension, uncontrolled diabetes mellitus, uncontrolled heart failure, tuberculosis, chronic kidney disease, immunocompromised state, osteoporosis, active peptic ulcer disease or uncontrolled gastro-oesophageal reflux, severe affective disorder or past history of drug-induced psychosis.

Screening assessments are listed below (and set out under the column headed 'Screening' in the Trial Assessments Table 3, Trial Assessments (Dose Escalation Phase, Paediatric Dose Confirmation Phase, and Immediate Treatment Arms of Dose Expansion Phase) and Table 4: Trial assessments (Deferred Treatment Group)):

1. Genetic testing (if unconfirmed at an accredited laboratory prior to screening)
2. Medical history and concomitant medication
3. Physical examination
4. Vital signs including blood pressure
5. Ocular examination
6. Visual acuity
7. Contrast sensitivity
8. Spectral Domain Optical Coherence Tomography (SD-OCT) (+/- Adaptive Optics (AO) imaging depending on age, as a greater degree of co-operation is needed compared to SD-OCT)
9. Visual Mobility

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 4 months prior to enrolment.

Historical images will be collected wherever possible, with written informed consent from the participants, in order to assess the slowing or halting of progression over time, and to compare the identical structural and functional assessments acquired prior to intervention and determine rate of change over time in this progressive disease. If genetic confirmation from an accredited laboratory has been obtained prior to the participant consenting to the trial this assessment does not to be repeated during screening.

5.3.1.6.3 Rescreening

Patients who have failed screening under a previous version of the protocol may be reconsidered for eligibility. All subjects who are rescreened must signed the updated ICF. Any tests that have been completed within 4 months of rescreening date will not need to be repeated.

5.3.1.6.4 Enrolment (Randomisation)

Participants who fulfil the study entry criteria based on the results of all screening assessments will be enrolled (randomised) in the trial. ATIMP will be administered within 3 months of enrolment for participants randomised to immediate treatment. If the ATIMP is not delivered within 3 months of enrolment, all screening tests with the exception of genetic testing, visual mobility and electrophysiological assessment will be repeated and eligibility for enrolment re-assessed[3]. For participants randomised to the control (deferred treatment) arm, study assessments will be performed per the Table 4: Trial Assessments (Deferred treatment arm).

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

5.4 Interventions

5.4.1 Products

5.4.1.1 Name and description of Investigational Medicinal Products

AAV2/5-hRKp.RPGR is an advanced therapy investigational medicinal product (ATIMP): specifically, a gene therapy product.

AAV2/5-hRKp.RPGR is a gene therapy product to be developed for the treatment of a form of retinitis pigmentosa caused by defects in the gene encoding RPGR. This is the retinitis pigmentosa GTPase regulator protein that plays an essential role in the structure and function of rod and cone photoreceptors. Disruption of the gene prevents normal translocation of phototransduction cascade proteins to the photoreceptor outer segment, leading to a phototransduction dysfunction and cell death. Recombinant adeno-associated virus (rAAV) mediated gene transfer of a copy of the normal *RPGR* gene to the photoreceptors, results in stable, long term transgene expression and improves photoreceptor survival and vision in rodents with *RPGR* gene defects.

AAV2/5-hRKp.RPGR consists of a linear single strand of DNA packaged in a rAAV protein capsid of serotype 5. The AAV2/5-hRKp.RPGR genome incorporates 290 nucleotides of the wild-type AAV2 ITR (Inverted

[3] For patients whose surgery dates were postponed due to COVID 19 please refer to appendix 1

Terminal Repeats) sequences that provide *in cis* the packaging signal, a cDNA encoding human *RPGR-ORF15*, driven by a human photoreceptor-specific genomic promoter (Rhodopsin Kinase, RK, *GRK1*). 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.

5.4.1.2 ATIMPs Classified as Genetically Modified Organisms

The ATIMP (AAV2/5-hRKp.RPGR) 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 USA must obtain Institutional Biosafety Committee approval in addition to Institutional Review Board (IRB) approval to administer recombinant nucleic acid molecule material to human participants.

5.4.1.3 Source of ATIMPs

The ATIMP has been manufactured at the [redacted] in accordance with current Good Manufacturing Practice for clinical trial materials.

5.4.1.4 Preparation and labelling of the ATIMP

Preparation and labelling of the ATIMP will be completed in accordance with the relevant GMP and national guidelines.

The ATIMP is a recombinant serotype 2/5 adeno-associated viral vector containing a human RPGR-ORF15 cDNA, with a 378 bp (in-frame) deletion in the purine-rich tract in the ORF15 region. The transgene is driven by a fragment of the human Rhodopsin Kinase promoter. The manufacturer [redacted] will perform analytical testing and provide certification. Aliquoting into vials and labelling of the ATIMP was the

responsibility of [redacted] The [redacted] was responsible for testing, release and storage of the final ATIMP. This responsibility for ATIMP storage and stability testing and subsequent expiry dating extension and labelling has been transferred to MeiraGTx.

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.

A detailed ATIMP management plan and manual describing the preparation of the vector prior to administration will be followed.

5.4.1.5 Description and Justification of Route of Administration and Dose

Efficient transduction of photoreceptor cells requires the ATIMP (AAV2/5-hRKp.RPGR) to be administered to the subretinal space.

Delivery of vector suspension to the subretinal space will be performed by standard surgical vitrectomy. This will involve a 3-port pars plana vitrectomy followed by injection of vector suspension using a fine cannula through small retinotomies into the subretinal space, resulting in a transient retinal detachment. Previous gene therapy clinical trials have shown that the bleb of subretinal vector suspension can be expected to resolve spontaneously over the course of the first 24 to 48 hours postoperatively as the fluid is absorbed by the underlying retinal pigment epithelium. Risks to visual function will be minimized by controlling the area of ATIMP delivery, and by leaving the contralateral eye untreated.

The highest ATIMP dose that is intended to be delivered to the trial participants is based on dose-limiting toxicity that was seen in an earlier trial of AAV2-mediated gene therapy for LCA2, where 1 mL of ATIMP at [redacted] was found to be the highest safe dose that could be administered subretinally. However, more recent data from a trial using AAV2/5 indicate that this serotype can elicit an inflammatory reaction to the dose of [redacted] that could pose a risk. As toxicity in this context is a complex interaction between local retinal effects, wider ocular effects and systemic effects, the decision was taken to use the confirmed safe volume (1 mL) and a titre of [redacted]. As AAV2/5-mediated transduction of photoreceptors in dogs and non-human primates is efficient over a wide range of titres, including lower titres than used in

this study we are confident that the RPGR transgene can be delivered to the photoreceptors effectively at [redacted].

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

1. Cefuroxime can be administered subconjuctivally at 50mg in 0.5ml normal saline, or 125mg in 1.0mL normal saline according to local practice. or cefazolin at 50 mg/0.5mL or vancomycin at 25 mg/0.5 mL antibiotic given at usual dose at end of surgery (standard (as per British National Formulary) dose as prophylaxis for post-operative infection) or any other antibiotic prescribed as per local hospital practices.
2. Long acting steroid in the sub-tenon space following sclerotomy closure according to local guidelines/standard of care.
3. Betamethasone can be administered subconjunctivally at 2mg - 5mg in 0.5mL, according to local practice. or dexamethasone can be administered subconjuctivally at 1.5mg- 2.0mg in 0.5mL, according to local practice.at end of surgery (standard dose as prophylaxis for post-operative inflammation)) or any other steroid prescribed as per local hospital practices.
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, then 2 times daily for a further 2 weeks (weeks 4 to 6) following ATIMP administration.
    - 3and 4 above will be administered to minimise inflammation and protect against infection postoperatively.
6. Omeprazole:
    - In adults 20mg per day for the duration of the steroid treatment
    - In children aged up to 16 weighing 5 kg to less than 10 kg (11 lb to less than 22 lb): 5 mg taken once per day for the duration of the steroid treatment
    - In children aged up to 16 weighing 10 kg to less than 20 kg (22 lb to less than 44 lb): 10 mg taken once per day for the duration of the steroid treatment
    - In children aged up to16 weighing 20 kg (44 lb) or more: 20 mg taken once per day for the duration of the steroid treatment
7. Prednisolone or Prednisone (oral steroid) as prophylaxis against potential intraocular immune responses:

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

Following the ATIMP administration as follows:

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

Children will be prescribed a tapering regimen of prednisolone tailored according to age and weight, and in addition intravenous methylprednisolone 30mg/kg on the day of surgery (maximum total no more than 1g). A further dose of methylprednisolone may be administered at week 4 in the presence of signs of intraocular inflammation. The regimen is described below:

- 0.5 mg/kg daily for one week **prior** to ATIMP administration
- 1 mg/kg daily for the first week following ATIMP administration
- 0.8 mg/kg daily for the second week following ATIMP administration
- 0.7 mg/kg daily for the third week following ATIMP administration
- 0.6 mg/kg daily for the fourth week following ATIMP administration
- 0.5 mg/kg daily for the fifth week following ATIMP administration
- 0.4 mg/kg daily for the sixth week following ATIMP administration
- 0.25 mg/kg daily for the seventh week following ATIMP administration
- 0.125 mg/kg daily for the eighth week following ATIMP administration
-

Following completion of steroid treatment, testing (if required), will be performed to confirm Hepatitis B viral load.

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 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 3: Trial assessments Dose Escalation Phase, Paediatric Dose Confirmation Phase, and Immediate Treatment Arms of Dose Expansion Phase and Table 4: Trial assessments Deferred Treatment Group). For assessments requiring multiple baselines, testing is preferred on separate days within a maximum 3-month period to allow for day-to-day variation and baseline variability for individual participants. However, it is acknowledged that a balance will be achieved between what is pragmatic and appropriate for the different tests on an individual basis. Each set of baseline measurements may take up to 3 days to perform in total in some instances, results for protocol specified baseline tests may be available through a subject's prior participation on the MGT011 RPGR natural history study or as a part of routine clinical examination. 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.

Baseline assessments will be completed as soon as possible after randomisation and will be valid for 3 months[4]. In the deferred treatment group, a day 0 will be applied at the end of baseline assessments and deferred treatment follow up will be calculated from this date.

Up to 10 mL of blood will be collected and to obtain serum samples in order to assess baseline levels of circulating antibodies against AAV serotype 5 and *RPGR* so that immunological responses to vector capsids and transgene product might be determined following vector administration (collectively described as serology in Table 3: Trial assessments). It is anticipated that the majority of participants will have no detectable pre-existing circulating antibodies against AAV5 or *RPGR*. The presence or absence of circulating antibodies will not affect recruitment of the participant. All serology tests will be performed at the Institutional Laboratory in the UK.

[4] For patients who surgery dates were postponed due to COVID 19 please refer to appendix 1

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:

1. Serological tests
2. Blood pressure
3. Haematology
4. Biochemistry
5. Hepatitis B testing**
6. Best corrected visual acuity and low luminance visual acuity
7. Contrast sensitivity testing
8. Ocular examination
9. Static visual field testing
10. Spectral-domain optical coherence tomography (SD-OCT)
11. Fundus autofluorescence imaging
12. Colour fundus photography
13. Full-field electroretinography (ERG)
14. Pattern electroretinography (PERG)
15. Visual mobility assessment
16. Patient-Reported Outcome (PRO) questionnaires
17. Treatment Experience Interview

** Hepatitis B testing will be performed if required by local practice

Tests that will be performed where possible are:

18. Mesopic and scotopic microperimetry
19. Detailed psychophysical/colour vision assessments
20. Multifocal electroretinography (mfERG)
21. Adaptive Optics imaging
22. Reading assessment

Further details of clinical assessments can be found in the *RPGR* XLRP study manual. Images taken at all timepoints will be sent for independent reading and analysis at centres in both the UK and US.

With the participant's consent, information collected during their assessments in the format of videos, pictures or similar may be sent to the site where the participant enrolled in the main part of the study, as study records. Copies of this non-identifiable information in the format of videos, pictures or similar may be sent to a third-party provider or to the sponsor and may be used for educational purposes.

(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) Patient-Reported Outcome (PRO) Assessments.

Patient-reported outcomes should be completed before any other assessments including physician assessments, treatment administration or provision of results in order to reduce the potential to influence the subject's response. The following patient- and clinician-reported outcomes will be assessed as outlined in Section 5.6 - Table 3: Trial assessments (Dose Escalation Phase, Paediatric Dose Confirmation Phase, and Immediate Treatment Arms of Dose Expansion Phase) and Table 4: Trial assessments (Deferred Treatment Group).

Participants will complete age appropriate versions of the Impact of Visual Impairment (IVI) vision-related quality of life (VRQoL) questionnaire, a Low Luminance Questionnaire (LLQ), an age appropriate EQ5D health-related quality of life (HRQoL) questionnaire (EQ-5D-5L or EQ-5D-Y), Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) items. A sample of each of the PROs and instructions for completion are provided in the PRO Completion guide.

Impact of Visual Impairment – Adult (IVI-A) Questionnaire

The IVI-A and IVI-C questionnaires assess vision-related quality of life (VRQoL) in adults and children (respectively) with low vision.

The IVI-A is a 28-item questionnaire comprised of three subscales: (i) mobility & independence, (ii) emotional well-being and (iii) reading & accessing information. (Lamoureux *et al.,* 2006) Response options include 3 and 4 -point Likert Scales (4 items are rated on a 3-point Likert scale: 0 = A lot; 1 = A fair amount; 2 = Not at all; the remaining items are rated on a 4-point Likert scale: 0 = A lot; 1 = A fair amount; 2 = A little; 3 = Not at all). An extra response option 'Don't do this for other reasons' (*excluded from analysis*) is possible for some items. The recall period is the last month. The IVI-A is scored by domain by taking the average of the items in each domain to obtain an IVI raw score (3 IVI raw scores in total). Higher IVI scores reflect greater visual ability/less vision-related quality of life impairment within the subjects.

Impact of Visual Impairment - Child (IVI-C) Questionnaire

The IVI-C is a 24-item questionnaire developed for use in children and adolescents that assesses the impact of vision loss on specific components of VRQoL, including orientation, mobility and social interaction (Cochrane *et al.,* 2008). Subjects are asked to rate the impact of visual impairment on a 5-point Likert scale: *always (5), almost always (4), sometimes (3), almost never (2), never (1),* and *no, for other reasons*.(Cochrane 2011). The final response is excluded from the analysis. The measure is unidimensional and a global score is calculated ranging from 0-120, with higher scores reflecting less vision impairment/greater vision-related quality of life. Six of the items are reverse scored to reduce response bias.

The Low Luminance Questionnaire (LLQ)

The Low Luminance Questionnaire (LLQ) is a 32-item disease-specific questionnaire for use in eye diseases to assess self-reported visual problems under low luminance and at night. The LLQ consists of six domains including Driving (5 items), Extreme lighting (8 items), Mobility (6 items), Emotional distress (4 items), General dim lighting (6 items), and Peripheral vision (3 items). Response options include 5- and 6-point Likert Scales ranging from “no difficulty at all” or “none of the time” to “stopped doing because of your vision”. Two additional response options represent non-applicable or missing data: “stopped for other reasons” and “don’t do”. The recall period is ‘at the present time’. Time to complete the measure is

approximately 5-10 minutes. The instrument is scored by domain, computed by scaling individual items from 0 to 100 and then averaging the individual items for each domain. A higher score reflects higher functional level (Owsley *et al.,* 2006).

EQ-5D Descriptive System

The EuroQol 5-Dimension (EQ-5D) Descriptive System is a standardized measure of health status. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care.

The EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The EQ-5D descriptive system is comprised of 5 items across the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and can be completed in 2-3 minutes. The EQ-5D-Y uses 3-point Likert response options and has 3 levels of severity for each dimension: No Problems, Some Problems and A Lot of Problems. The EQ-5D-5L uses 5-point Likert response options and has 5 levels of severity: No problems, Slight problems, Moderate problems, Severe problems, and Extreme problems. The recall period is 'Today'. Respondents are asked to indicate their health by placing a cross in the box next to the response that best represents their current health for each of the 5 dimensions. This results in a 1-digit number expressing the level of severity selected for that dimension. The responses for the 5 dimensions can be combined into a 3-digit number (for the EQ-5D-Y) or 5-digit number (for the EQ-5D-5L) describing the respondent's health state (e.g. 11233). The EQ-5D-5L health states, defined by the EQ-5D descriptive system, can be converted into a single index value using country-specific value sets. Index values range from 0 to 1, with higher scores representing better health-related quality of life. The index value facilitates the calculation of quality-adjusted life years (QALYS) that are used to inform economic evaluations of health care interventions. Country-specific value sets are not available for the EQ-5D-Y so an index value cannot be calculated for the child subjects.

The EQ-5D also includes a 20cm visual analog scale (EQ VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively. For the EQ-5D-Y, respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ VAS which best represents their own health on that day. For the EQ-5D-5L, respondents are asked to mark an X at that point on the EQ VAS which best represents their own health

on that day, and entering the number they marked on the line into the box. This can be used as a quantitative measure of health outcome that reflects the patient's own judgement. Completion of the EQ-5D instruments will take approximately 2-3 minutes.

Patient Global Impression of Severity (PGIS)

The Patient Global Impression of Severity (PGIS) is a 1-item questionnaire based on the clinical global impression scale developed by Guy (1976), designed to assess a patient's impression of disease severity. The PGIS asks the patient to select the one response, ranging from 'No Symptoms' to 'Very Severe', that best describes the overall severity of their retinitis pigmentosa 'at this time'

Completion will take approximately 1 minute or less. The PGIS will be assessed at baseline and at 3, 6 and 12 months post-treatment administration (for the low and intermediate-dose group), and at baseline and at 3 and 6 months post-treatment administration (for the deferred treatment group). The PGIS will be evaluated for change over time and used to validate change over time reported on the Patient Global Impression of Change (PGIC) item, to mitigate any potential recall bias on the PGIC.

Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change (PGIC) is a one-item patient-reported measure of perceived change in the patient's health condition following a study/treatment intervention. The PGIC assesses the extent to which a person's health condition has improved, worsened or remained unchanged since the start of their treatment using a scale ranging from 1 = Very much improved to 7 = Very much worse (where 4 = No change). The instructions ask the subject to select the one response that best describes the overall change in their retinitis pigmentosa since treatment was administered. Completion will take approximately 1 minute or less. The PGIC will be assessed at 3, 6 and 12 months post-treatment administration (for the low- and intermediate-dose group), and at 3 and 6 months post treatment administration (for the deferred treatment group).

Clinician Global Impression of Change (CGIC)

The Clinician Global Impression of Change (CGIC) is a generic global measure of change in a patient's health status assessed by a clinician following a study/treatment intervention. The CGIC asks the clinician to rate on a scale from 1 (=very much improved) to 7 (=very much worse) the overall change in the patient's retinitis pigmentosa since treatment was initiated. The CGIC will be assessed at 3, 6 and 12

months post-treatment administration (for the low- and intermediate-dose group), and at 3 and 6 months post treatment administration (for the deferred treatment group).

Treatment Experience Interview

Treatment experience interviews will be administered to all study participants. Subjects in the low- and intermediate dose active treatment group will participate in two interviews: one interview will be conducted at the month 6 / Visit 14 study visit (6 months post-treatment), and the second interview will be conducted at or within 14 days of the month 12/Visit 16 study visit (12 months post-treatment), or upon early withdrawal. The deferred treatment group subjects will participate in one interview at or within 14 days of the month 12 /Visit 16 study visit (6 months post-treatment), or upon early withdrawal. The questions included in the interview will be designed to more fully understand the subject's experience with the study treatment, the aspects of the condition that are most important to them, and the perceived efficacy of the study treatment. The interview will be conducted by telephone and will last 15 to 20 minutes. Subjects will be asked to consent to the treatment experience interview within the study informed consent form (ICF).

A specialist contract research organisation (CRO) will be commissioned to conduct the treatment experience interview sub-study. The study site will facilitate scheduling of the interviews, and the CRO will conduct the interviews by telephone using an experienced qualitative interviewer. For the month 12/ Visit 16 study visit interviews, the interviews may be conducted at the study site during the final study visit, or the subject may participate from their home within 14 days of the final study visit. Interviews will be audio recorded for the purposes of accurate transcription and analysis. The interviews will be transcribed by a third-party transcription agency. The transcripts will have any personally identifying information removed and any errors corrected, after which the audio recording will be permanently deleted by both the CRO and the transcription agency, and the interview transcript will serve as the source document.

The qualitative data collected during the patient treatment experience interviews will be analysed by the CRO and summarised in a final report.

(iii) Functional Assessments

Reading ability including reading acuity, maximum reading rate, and critical print size will be assessed.

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 microperimetry (mesopic and scotopic). The retinal locus of fixation will also be determined using microperimetry.

Full-field electroretinography (ERG), pattern ERG (PERG) and multifocal ERG (mfERG) will be performed according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards to assess both generalised retinal (rod and cone systems) and isolated macular function. Modified ISCEV protocols may be necessary in young children using internationally recognised modified protocols. 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 CRF. Consent to record the surgery will be requested of the participant. Intraocular surgery will be recorded using a video camera via the operating microscope as described in the consent process. Relevant recordings and images will be stored alongside the trial database.

5.4.2.2.1 Pre-operative procedure

For prophylaxis against potential intraocular immune responses to the ATIMP, participants will be prescribed a course of daily oral prednisolone commencing at a dose of 30mg daily for one week prior to ATIMP administration.

Preoperative procedures and intraocular administration of ATIMP will be as described in the Gene Therapy for X linked RPGR Study Manual.

5.4.2.2.2 Operative procedure

In the dose escalation and dose confirmation in paediatric participants phases of the study, the choice of eye for ATIMP administration will be the poorer-seeing eye as identified by the participant and CI/PI taking account of ocular dominance and visual acuity. In the randomised expansion phase, the eye to be

administered vector will be determined via randomisation to preserve objectivity. In order for this to be safely performed participants are required to have relatively symmetrical visual acuity.

The recombinant vector will be delivered in the form of a suspension of viral vector particles injected intraocularly (subretinally) under direct observation using an operating microscope. This procedure will include a 3-port pars plana vitrectomy followed by injection of ATIMP using a fine cannula through small retinotomies into the subretinal space.

Surgery will be performed under general anaesthesia. The eye and face will be prepared using povidone iodine solution as per routine intraocular surgery. The face and eye will be covered with an adhesive sterile plastic drape. An opening will be made at the point of the palpebral fissure (when applicable) 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. 3 pars plana sclerotomies will be sited to enable intraocular infusion, endoillumination probe and surgical instruments. The fundus will be viewed by means of a wide field indirect viewing system or a contact lens. To minimise the possibility of unplanned retinal detachment or preretinal fibrosis, vitrectomy (aspiration of vitreous gel) will be performed using a disposable cutter.

Intraocular administration of the viral vector suspension (AAV2/5-hRKp.RPGR) 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. 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 antibiotic and steroid 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 experience, it is anticipated 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 1st postoperative day, a full clinical ocular examination will be performed. Visual acuity, intraocular pressure, the degree of postoperative intraocular inflammation and the area of any residual retinal bleb will be documented. Fundus photography, 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 and then bd for a further 2 weeks) will be prescribed to minimise inflammation and protect against infection postoperatively.

Intraocular pressure of greater than 30 mmHg will be managed with systemic therapy where indicated with specialist advice sought as required.

Participants will be maintained on oral prednisolone (or other as appropriate) for 8 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 3, Trial Assessments (Dose Escalation Phase, Paediatric Dose Confirmation Phase, and Immediate Treatment Arms of Dose Expansion Phase) and Table 4: Trial assessments (Deferred Treatment Group)

Both safety and efficacy of the ATIMP will be evaluated at various time points up to 12 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 collected to obtain serum samples 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.

(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) for patients in the immediate treatment arm at baseline 1, prior to intraocular ATIMP administration and day 1, week 1, week 2, week 4,week 6 and week 9 following intraocular ATIMP administration. For patients on the deferred treatment arm at baseline 1, month 6 prior to intraocular ATIMP administration and day 1, week 1, week 2, week 4, week 6 and week 9.

(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 5.6 for details) to allow direct comparison of the data sets. These assessments will be scheduled over a period of a day for visits at day 1, day 3, day 7, week 2, week 4, week 6, and week 9 after surgery, and up

to 4 days for baseline examinations, and 3 months, 6 months, 9 months and 12 months following ATIMP administration. For the deferred treatment arm, assessments will be performed at day 1, day 3, day 7, week 2, week 4, week 6, week 9, month 3 and month 6 after surgery. For day 1 and 3, refraction cannot reliably be measured. Therefore, the most recent refraction measurement will be used.

All participants (adults and children) will need to be able to perform reliable visual acuity testing, SD-OCT, retinal sensitivity testing (static visual fields, and visual mobility assessment, 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 participant may be discontinued for that participant. This is not anticipated for the aforementioned key clinical assessments 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

Serum will be processed to investigate any immune responses to the ATIMP:

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

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

Whole blood will be processed at the [redacted], or a CLIA-accredited molecular diagnostic laboratory in the US, for *RPGR* mutation screening. Haematology and biochemistry samples and screen will be carried out at the [redacted], or an accredited laboratory in the US (Table 2 Haematology and Biochemistry).

Table 2: Haematology and Biochemistry

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 Investigational Medicinal Product

[redacted].

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

5.4.4 Dosage and dosage modifications

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

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

The ATIMP will be diluted as appropriate for the specific dose intended immediately prior to intraocular administration in Hartmann's solution at the time of administration. The CI/PI will prepare the appropriate dilution, and this will be checked in the operating theatre by a second individual prior to administration. The check will be recorded in the patient's source data notes.

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

5.4.5 Accountability

The ATIMP will be prescribed and handled according to the ATIMP management plan applicable for the site.

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

i. date
ii. participant identification
iii. batch number
iv. volume and dose of ATIMP administered
v. name of CI/PI administering ATIMP
vi. ATIMP name/code
vii. Trial reference code
viii. Expiry date

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

A system will be set-up to ensure the traceability of the ATIMP from the starting material, through to administration to the participant and destruction. A comprehensive ATIMP management plan and associated forms will be in place to ensure that the required accountability and traceability data is 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, should be used with caution, and appropriately documented on study logs where used. All concomitant medications (including steroids) must be recorded in the CRF from the day of informed consent.

5.4.8 Overdose of Trial Medication

A single intraocular administration of ATIMP will be performed by the operating surgeon (CI or a delegated vitreo-retinal surgeon). The volume of vector delivered to the target site will be measured by the syringe plunger scale 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 Treatment Discontinuation

5.4.9.1 Participant withdrawal

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

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial participation at any time without penalty or loss of benefits to which they would otherwise be entitled.

Although not obliged to give a reason for discontinuing their participation, a reasonable effort should be made to establish this, whilst remaining fully respectful of the participant's rights.

Should a participant withdraw from the study, a withdrawal CRF documenting the reason for withdrawal will be completed, in addition to the procedures and CRF for the final visit (12 month) assessments, with the participant's consent. However, participants will be encouraged to participate in any of the planned schedule for the trial whilst arranging a visit for routine (annual) clinical follow-up.

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

5.4.9.2 Trial Stopping Rules

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

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

5.5 Outcomes

5.5.1 Primary Outcomes

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

- Reduction in visual acuity by 15 ETDRS letters or more

- Severe unresponsive inflammation
- Infective endophthalmitis
- Ocular malignancy
- Grade III or above non-ocular SUSAR (see section 5.11.3)

5.5.2 Secondary Outcomes

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

- Slowing or halting of progressive deterioration in retinal structure or visual function that is greater than the baseline variation for that test and is sustained for at least 2 consecutive assessments. Slowing or halting of progression over time may be facilitated by comparing identical structural and functional assessments acquired prior to intervention/injection to better determine rate of change over time in this slowly progressive disease.

  Historical images will be collected wherever possible with written informed consent from the participants
- 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 baseline variation and measurable by electrophysiology (pattern ERG, multifocal ERG or full-field ERG).
- Health- and Vision-Related Quality of life (HRQoL, VRQOL) will be assessed by the Impact of Visual Impairment (IVI) questionnaire, the Low Luminance Questionnaire (LLQ), the EQ5D HRQoL questionnaire (EQ-5D-5L or EQ-5D-Y), changes in disease severity and health status will be assessed by the Patient Global Impression of Severity (PGIS), the Patient Global Impression of Change (PGIC) and the Clinician Global Impression of Change (CGIC) measures.

5.6 Trial Assessments

Table 3: Trial assessments (Dose Escalation Phase, Paediatric Dose Confirmation Phase, and Immediate Treatment Arms of Dose Expansion Phase)*

	Screening	Randomisation	Baseline[1, 2]			ATIMP admin	D1	D3	W1	W2	W4	W6	W9	M3	M6	M9	M12
Flexibility of schedule (± days)	Up to 4 months prior to randomisation		- 3 months			Day 0	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 7D	± 14D	± 14D	± 14D	± 14D
Visit number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Informed consent	•																
Physical exam	•																
Medical history	•								•	•	•	•	•	•	•	•	•
Eligibility determination	•																
IMP administration						★											
Adverse event review			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant medication review	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Genetic screening	•																
Vital signs (including height and weight)[3]	•		•				•	•	•	•	•	•	•				
Randomisation		★															
Haematology			•				•		•	•	•	•					
Biochemistry/glucose			•				•		•	•	•	•	•[7]				
Hepatitis B (HBV) testing [6]	•												•				
Serology			•								•			•	•		
PCR							•				•						
QoL questionnaires (IVI and EQ5D-5L and EQ5D-Y, Low Luminance Questionnaire) Patient Global Impression of Severity			•											•	•		•

	Screening Up to 4 months prior to randomisation	Randomisation	Baseline[1, 2]			ATIMP admin	D1	D3	W1	W2	W4	W6	W9	M3	M6	M9	M12
Flexibility of schedule (± days)			- 3 months			Day 0	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 7D	± 14D	± 14D	± 14D	± 14D
Patient Global Impression of Change and Clinician Global Impression of Change														•	•		•
Treatment Experience Interview[9]															•		•
Visual acuity[4]	•		•	•	•		•	•	•	•	•	•	•	•	•	•	•
Low Luminance Visual Acuity			•	•	•									•	•	•	•
Contrast sensitivity	•		•	•	•									•	•	•	•
Reading speed			•	•	•									•	•	•	•
Colour vision assessments			•	•	•									•	•		•
Static visual fields			•	•	•									•	•		•
Microperimetry			•	•	•									•	•		•
Ocular examination	•		•	•	•		•	•	•	•	•	•	•	•	•	•	•
Fundus photography			•				•	•	•	•	•	•	•	•	•	•	•
Optical coherence tomography	•		•	•	•		•	•	•	•	•	•	•	•	•	•	•
Adaptive optics imaging			•												•		•
Fundus autofluorescence			•	•	•									•	•		•
Full field electroretinography[5]			•												•		•
Pattern electroretinography[5]			•												•		•
Multifocal electroretinography[5]			•												•		•
Visual mobility assessment[8]	•													•	•		•

[1]Baseline assessments may be performed on the same day where considered logistically and clinically appropriate. All assessments should be performed as soon as possible; however, all baseline assessments must be done within a 3 month period.

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

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

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

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

[6] HBV testing is only mandatory for participants if required by local practice. Participants with chronic hepatitis B virus infection as indicated by detectable surface antigen will be excluded from the study. For those with negative surface antigen, but positive hepatitis B core antibody, testing will be performed to confirm Hepatitis B viral load following completion of steroid treatment.

[7] Additional monitoring of liver enzymes will be performed following steroid treatment

[8] Patients who screened failed under a previous version of the protocol may be reconsidered for eligibility and will not be required to repeat tests provided these were performed within the visit window from the original screening date.

[9] Two Treatment Experience interviews will be administered to the low and intermediate dose active treatment group at 6 months (Visit 14) and at 12 months post-treatment (either at the visit or within 14 days of the final study visit - visit 16), or upon early withdrawal.

*Per section 5.4.2.1 assessments listed as “performed in all participants” must be performed, every effort must be made to perform all other assessments where possible

Table 4: Trial Assessments (Deferred Treatment arm) *

	Screening Up to 4 months prior to randomisation	Randomisation	Baseline[1, 2]			M3[8]	M6[8]	ATIMP admin after M6 assessments	D1 post-ATIMP admin	D3 post-ATIMP admin	W1 post-ATIMP admin	W2 post-ATIMP admin	W4 post-ATIMP admin	W6 post-ATIMP admin	W9 post-ATIMP admin	M3 post ATIMP admin	M6 post ATIMP admin
Flexibility of schedule (± days)						± 14D	14D	+14D	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 7D	± 14D	± 14D
Visit number	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Informed consent	•																
Physical exam	•						•										
Medical history	•					•	•				•	•	•	•		•	•
Eligibility determination	•						•										
IMP administration								★									
Adverse event review			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant medication review	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Genetic screening	•																
Vital signs (including height and weight)[3]	•		•				•		•	•	•	•	•	•	•		
Randomisation		★															
Haematology			•				•		•		•	•	•	•			
Biochemistry/ glucose			•				•		•		•	•	•	•	•[7]		
Hepatitis B (HBV) testing [6]	•														•		
Serology			•										•			•	•
PCR									•				•				

	Screening Up to 4 months prior to randomisation	Randomisation	Baseline[1, 2]			M3[8]	M6[8]	ATIMP admin after M6 assessments	D1 post-ATIMP admin	D3 post-ATIMP admin	W1 post-ATIMP admin	W2 post-ATIMP admin	W4 post-ATIMP admin	W6 post-ATIMP admin	W9 post-ATIMP admin	M3 post ATIMP admin	M6 post ATIMP admin
Flexibility of schedule (± days)						± 14D	14D	+14D	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 7D	± 14D	± 14D
QoL questionnaires (IVI, EQ5D-5L, EQ5D-Y, Low Luminance Questionnaire), Patient Global Impression of Severity			•				•									•	•
Patient Global Impression of Change and Clinician Impression of Change																•	•
Treatment Experience Interview[10]																	•
Visual acuity[4]	•		•	•	•	•	•		•	•	•	•	•	•	•	•	•
Low Luminance Visual Acuity			•	•	•											•	•
Contrast sensitivity	•		•	•	•	•	•									•	•
Reading speed			•	•	•	•	•									•	•
Colour vision assessments			•	•	•	•	•									•	•
Static visual fields			•	•	•	•	•									•	•
Microperimetry			•	•	•	•	•									•	•
Ocular examination	•		•	•	•	•	•		•	•	•	•	•	•	•	•	•
Fundus photography			•			•	•		•	•	•	•	•	•	•	•	•

	Screening Up to 4 months prior to randomisation	Randomisation	Baseline[1, 2]			M3[8]	M6[8]	ATIMP admin after M6 assessments	D1 post-ATIMP admin	D3 post-ATIMP admin	W1 post-ATIMP admin	W2 post-ATIMP admin	W4 post-ATIMP admin	W6 post-ATIMP admin	W9 post-ATIMP admin	M3 post ATIMP admin	M6 post ATIMP admin
Flexibility of schedule (± days)						± 14D	14D	+14D	± 0D	± 1D	± 2D	± 4D	± 7D	± 7D	± 7D	± 14D	± 14D
Optical coherence tomography	•		•	•	•	•	•		•	•	•	•	•	•	•	•	•
Adaptive optics imaging			•				•										•
Fundus autofluorescence			•	•	•	•	•									•	•
Full field electroretinography[5]			•			•											•
Pattern electroretinography[5]			•			•											•
Multifocal electroretinography[5]			•			•											•
Visual mobility assessment[8 9]	•					•	•									•	•

[1]Baseline assessments may be performed on the same day where considered logistically and clinically appropriate. All assessments should be performed as soon as possible however all baseline assessments must be done within a 4 month period.

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

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

[4] Visual acuity at day 1 and 3 post-ATIMP administration will be assessed using the previous refraction.

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

[6] HBV testing is only mandatory for participants if required by local practice. Participants with chronic hepatitis B virus infection as indicated by detectable surface antigen will be excluded from the study. For those with negative surface antigen, but positive hepatitis B core antibody, testing will be performed to confirm Hepatitis B viral load following completion of steroid treatment.

[7] Additional monitoring of liver enzymes will be performed following steroid treatment

[8] Month 3 and 6 assessments should be planned for +3 months and +6 months after the last baseline assessment (Baseline visit 4)

[9] Patients who screened failed under a previous version of the protocol may be reconsidered for eligibility and will not be required to repeat tests provided these were performed within the visit window from the original screening date.

[10] Treatment Experience interviews will be administered to all subjects either at or within 14 days of the final study visit (month 6 / visit 16), or upon early withdrawal.

*Per section 5.4.2.1 assessments listed as “performed in all participants” must be performed, every effort must be made to perform all other assessments where possible

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. 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 12 months following ATIMP administration. The MHRA will be notified of the end of the trial within 90 days of its completion.

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

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

5.7 Sample Size

This is a Phase I/II trial to establish safety and assess indicators of potential efficacy of the ATIMP, therefore there is no formal sample size calculation. The trial will enrol up to 71 participants (up to 18 in the dose escalation phase, up to 5 in the dose confirmation in paediatric phase, and up to 48 in the randomised expansion phase), as described in section 4.3.2.2. We estimate that inclusion of up to 53 participants will be sufficient to determine the safety and tolerability of the intervention.

5.8 Recruitment and Retention

5.8.1 Recruitment

Participants will be recruited through research sites in the US and in the UK 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 71 participants within a period of 48 months.

5.8.2 Retention

Participants will be supported to remain in follow-up by regular contact as per the protocol and the 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 ofAAV2/5-hRKp.RPGR to 1 eye. The dose received by each participant will depend on the order of their enrolment in the trial according to the sequence of dose escalation, and the extent of dose-limiting events. Children will not be enrolled in the trial until the safety profile and recommended dose have been established in adults.

In the randomised expansion phase, a target of up to 48 eligible participants will be randomised in a 1:1:1 ratio to receive immediate low dose administration (n=up to 16), immediate intermediate dose administration (n=up to 16) or deferred administration (n=up to 16). Within the deferred administration treatment group, participants will be further randomised in a 1:1 ratio to deferred low dose administration (n=up to 8) or deferred intermediate dose administration (n=up to 8). The randomisation of treatment will be stratified by age at informed consent (<25 years, ≥25 years), the rationale for the stratification levels is described in Section 4.3.2.2.5 of this document. Thus, the overall randomisation ratio will be 2:2:1:1 (immediate low dose: immediate intermediate dose: deferred low dose: deferred intermediate dose).

The eye of treatment will also be randomised in a 1:1 ratio; this aspect of the randomisation is considered administrative so will not be stratified or balanced across treatment groups, the rationale for this is described in Section 5.4.2.2.2 of this document.

The randomisations will be produced by an independent statistician. The treatment and eye will be allocated in the web-based EDC system.

5.10 Data Collection, Management and Analysis

5.10.1 Data collection, management and entry

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

Data will be captured in a fully validated, 21 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.

5.10.2 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 (12 month) assessments with the participant's consent.

5.10.3 Statistical Methods

5.10.3.1 Statistical Analysis Plan

A formal Statistical Analysis Plan (SAP) will be written by the sponsor and approved by the IDMC. This trial is an open label, no crossover, phase I/II trial involving a small number of participants, and analysis of the primary and secondary outcomes will be descriptive in nature.

5.10.3.2 Statistical Methods – Outcomes

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

- Reduction in visual acuity by 15 ETDRS letters or more
- Severe unresponsive inflammation (defined below)

- 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.

Safety data relating to participants at all dose levels 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) Slowing or halting of progressive deterioration in retinal structure or visual function that is greater than the baseline variation for that test and is sustained for at least 2 consecutive assessments.
2) Any improvement in visual function from baseline that is greater than the baseline variation for that test and is sustained for at least 2 consecutive assessments.
3) Any improvement in retinal function from baseline that is measurable by electroretinography (ERG)

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

Health- and vision-related quality of life (HRQoL, VRQoL) patient reported outcome and treatment experience interview data will be used to correlate a participant's feeling about their own wellbeing with clinical observations.

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

5.10.3.4 Economic evaluations

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

5.11 Data Monitoring

5.11.1 Independent Data Monitoring Committee

To ensure the safety and efficacy and overall trial conduct, an Independent Data Monitoring Committee (IDMC) will be established and take part in the data monitoring. The IDMC will consist of members with specific expertise in ophthalmology and molecular genetics. The IDMC will make recommendations on the safety data prior to any dose change, and prior to the first participant aged under 16 in the UK or under 18 in the US, being dosed in the trial.

Further details of the roles and responsibilities of the IDMC, including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the *RPGR* XLRP IDMC Charter.

5.11.2 Interim Analyses

An interim analysis may be scheduled when all patients in the immediate treatment arms (n= up to 32) of the randomised expansion phase of the trial reach 3 and 6-months post-surgery.

5.11.3 Data Monitoring for Harm

5.11.3.1 Safety reporting

[redacted] will be responsible for pharmacovigilance services.

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

Table 5: 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 (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 administration of the trial treatment

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

5.11.3.2 Other Notifiable Adverse Events

In order to manage the safety risks associated with administration of the vector, all safety events will be reviewed within a short time frame for all participants, as described in the trial Data Management Plan.

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

Although participants are instructed to use barrier and spermicide contraception, we cannot exclude entirely that the partner of a participant might become pregnant after administration of the ATIMP. In the unlikely event that this occurs we will notify the participant's GP that he is participating in a gene therapy trial and that, although the risks involved are minimal, there is a chance of gene transfer to the unborn child. With the participant's consent, we will contact the partner to ascertain the status of the pregnancy and the outcome. The pregnancy will be reported to [redacted] on a pregnancy report form within 24 hours of the investigator becoming aware of the event.

5.11.3.4 Investigator responsibilities relating to safety reporting

The Investigator will assume overall responsibility for evaluating and reporting adverse events. In urgent situations a member of the trial team may report on their behalf, while making every effort to discuss the event with them. All non-serious AEs and ARs, whether expected or not, should be recorded in the participant's medical notes and adverse events 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 CMT. SAEs should be notified to [redacted] immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

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

All serious adverse events will be recorded in the hospital notes and on a paper SAE form. 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 if this extends beyond the end of the study. All SAEs will be recorded, fully investigated and appropriately managed until resolution or stabilisation and CI sign off.

5.11.3.4.1 Seriousness assessment

When an AE or AR occurs, the investigator responsible for the care of the participant must assess whether or not the event is serious using the definition given in Table 5: Adverse Event Definitions. If the event is classified as 'serious' then an SAE form must be completed and emailed to [redacted] (or delegated body) within 24 hours.

5.11.3.4.2 Severity or grading of Adverse Events

The severity of all AEs in this trial should be graded using the toxicity gradings in NIH CTCAE Version 4.0 (NIH 2009) (Table 6: Grading of Adverse Events).

Table 6: 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.

5.11.3.4.3 Causality

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

- The ATIMP administration surgery
- The ATIMP

The differentiated causality assessments will be captured in the trial specific CRF and SAE form using the definitions in Table 7: Causality Definitions.

Table 7: 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

For each AE/SAE, a causality assessment for the ATIMP administration surgery must also be provided. Any events related to the surgery alone will not be reported to the relevant regulatory agencies.

5.11.3.4.4 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 8: Assessment of expectedness

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

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

The reference document to be used to assess expectedness against the ATIMP and surgery is the Investigator Brochure. Procedure-related adverse events cannot be considered attributable to the ATIMP.

Previous experience with AAV-mediated gene therapy in the retina indicates that the risks are largely limited to the eye. A temporary and/or mild decrease in visual acuity, due to detachment of the retina or post-surgical inflammation, is to be expected after intraocular surgery and will not cause undue discomfort to the participants. Therefore, we have defined the success criteria for the primary outcome for 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

5.11.3.5 Notifications

5.11.3.5.1 Notifications by the Investigator to [redacted]

All adverse events will be recorded in the participant's medical notes and the CRF from the date of written informed consent until last study visit. [redacted] must be notified of all SAEs and SUSARs within 24 hours of the investigator becoming aware of the event during this period. The investigator will respond to any SAE queries raised by [redacted] as soon as possible. After last visit, any SAE reported to the investigator and considered causally related to trial treatment should be reported as part of the follow up study. For any participants that do not go into the follow up study, then SAEs that occur after the end of the trial and that may be attributed to ATIMP administration should be reported to the relevant regulatory agencies.

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, and causality of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes

necessary, sign and then email to [redacted]. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

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

The SAE form must be scanned and sent by email to the trial team on [redacted]

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

5.11.3.5.2 [redacted] responsibilities

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

5.11.3.5.4 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.

5.11.3.5.5 Annual Progress Reports

An annual progress report (APR) will be submitted 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.

5.11.4 Quality Assurance and Control

5.11.4.1 Risk Assessment

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

5.11.4.2.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, research ethics committee (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.

5.11.4.3 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, and eligibility; adherence to trial intervention 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.

5.11.4.3.1 Independent Data Monitoring Committee

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

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the Health Research Authority (HRA) for approval and to the relevant REC/IRB 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 USA).

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

This is a Clinical Trial of an Investigational New Drug as defined by 21 CFR 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 site's Institutional Biosafety Committee.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be submitted to the Regulatory Authorities 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 relevant local department of each participating site or to other local departments for approval as required in each country. A copy of the local approval 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 (e.g. 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.

6.5 Consent or Assent

Potential participants will be provided with a Participant Information Sheet (PIS) and given time to read it fully. Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and

unambiguously clear that the participant (or parent or guardian of a child) is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment (or that of their child).

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

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

6.6 Confidentiality

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

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

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

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

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

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

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

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

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 for consultancy services.

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

6.8 Indemnity

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

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

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

6.9 Finance

The trial is fully funded by MeiraGTx UK II Ltd. It is not expected that any further external funding will be sought.

6.10 Archiving

6.10.1 Archiving of essential trial documentation relating to traceability

Requirements for a traceability system and document archiving will be met in line with Regulation 1394/2007 on Advanced Therapy Medicinal Products and the applicable Directives therein. To comply with the regulatory requirements, each responsible party (the sponsor of the trial, the manufacturer and the investigator(s)/institution(s) where the ATIMP is used) will ensure that the information relating to the traceability and accountability, from the production of ATIMPs to the recipient (participant) receiving the ATIMPs, are archived for a minimum of 30 years after the expiry date of the ATIMP. These requirements will be set out in contractual agreements between the parties and the sponsor.

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

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

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

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

6.10.2 Archiving of Other Essential Trial Documentation

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

further notice. Archiving of REC/IRB notices should be maintained according to local and/or institutional requirements.

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

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

Destruction of essential documents will require authorisation from the Sponsor.

6.11 Access to Data

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

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

6.12 Ancillary and Post-trial Care

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

6.13 Publication Policy

6.13.1 Trial Results

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

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

7 Ancillary Studies

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

8 Appendix 1: Guidance on Study Conduct during the COVID-19 Pandemic

The measures outlined in this Appendix are temporary, while access to sites is restricted during the COVID 19 pandemic. 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 recognized 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.

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 EDC for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix “COVID-19-related” in the case report form (CRF).

Scheduled visits that cannot be conducted in person at the study site will be performed remotely/virtually, and site -based evaluations may be delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy and safety endpoint assessments should be performed as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

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 summarized 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	Patient missing any scheduled visits	If scheduled visits cannot be conducted within the visit window the site can schedule an additional visit at the earliest opportunity the patient is able to travel,
4	Baseline Assessments	Baseline assessments for those patients who have had surgery postponed due to COVID 19 - these baseline assessments will be valid up to 6 months expect for Haematology, Biochemistry and Glucose which will need repeating.
5	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 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.

		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 carer 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 event occurring. Reminder of importance to report any new AEs/symptoms to be communicated to patients by the sites during this time.
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 Version 1	NA
Protocol Version 2 10 March 2017	To incorporate the flow chart for the dose escalation, dose of drugs used at the time of administration of the ATIMP and reconsenting the children as they progress through the age brackets.
Protocol Version 3 12 April 2017	To extend the course of post-surgery prophylactic steroids from 4 weeks to 8 weeks. Consequently, the duration for considering dose limiting events has been extended from 6 weeks to 9 weeks to cover the period of steroid administration and one additional week and other minor clarifications
Protocol Version 4 25 May 2017	To add additional 2 exclusion criteria, and to refer to a barrier and spermicide form of contraception, rather than double barrier method and also to clarify that only males will be included in the trial
Protocol Version 5 13 November 2017	To update the medium and high dose. To reduce the gap between participant 1 and 2/3 in a cohort from 9 weeks to 4 weeks and update the prophylactic post-administrative steroid regimen in children, and clarify safety reporting and confirmatory safety dose for children
Protocol Version 6 27 February 2018	To clarify the allowance of data obtained from the natural history study be used for screening and or baseline assessments (with consent from subjects) in order to avoid unnecessary testing of subjects. Clarify that more than 1 surgeon at a site may inject vector
Protocol Version 7.0 26 April 2018	To clarify number of visual mobility assessments required To reduce the specificity of anti-biotics that may be prescribed on the trial.
Protocol Version 7.1 19 September 2018 (MEEI Specific)	This amendment was specific to Massachusetts Eye and Ear Institute to include the need for Hepatitis B screening.
Protocol Version 9.0 11 February 2019	To include a randomised component to the expansion phase of the study To include further QOL measurement tool To reduce the follow up from 18 to 12 months

	To include an Interim Analysis at 3 and 6 months post treatment for patients in the low/intermediate dose treatment arms of the randomised component of the trial
Protocol Version 10.0 09 August 2019	To amend and clarify the inclusion and exclusion criteria for the trial To remove FST at all assessments and to remove ERG at screening to reduce the assessment burden on patients To add in Low Luminance Visual Acuity testing To include additional Patient Reported Outcomes and to add a Clinician Reported Outcome. To include Treatment Experience interviews. To correct minor errors in the Patient Visit Schedule
Protocol v11.0 01 May 2020	Included guidance on the management of patients during COVID 19 pandemic Corrected minor errors in the protocol v10.0 Updated Steroids risks Included update local steroid use

10 References

Annear MJ, Bartoe JT, Barker SE, Smith AJ, Curran PG, Bainbridge JW, Ali RR, Petersen-Jones SM. Gene therapy in the second eye of RPE65-deficient dogs improves retinal function. Gene Ther. 2011 Jan;18(1):53-61. doi: 10.1038/gt.2010.111. Epub 2010 Aug 12.

Bainbridge JWB, Smith AJ, Barker SS *et al*. Effect of gene therapy on visual function in Leber's Congenital Amaurosis. N Engl J Med 2008; 358(21):2231-2239.

Balaggan KS, Duran Y, Georgiadis A et Al. Absence of ocular malignant transformation after sub-retinal delivery of rAAV2/2 or integrating lentiviral vectors in p53-deficient mice. Gene ther, 2012, 19(2):182-8.

Barker SE, Broderick CA, Robbie SJ, Duran Y, Natkunarajah M, Buch P, Balaggan KS, MacLaren RE, Bainbridge JW, Smith AJ, Ali RR. Subretinal delivery of adeno-associated virus serotype 2 results in minimal immune responses that allow repeat vector administration in immunocompetent mice. J Gene Med. 2009 Jun;11(6):486-97. doi: 10.1002/jgm.1327.

Chan AW, Tetzlaff JM, Altman DG et Al. SPIRIT 2013 Statement: Defining Protocol Items for Clinical Trials. *Ann Intern Med*2013; 158:200-207.

Chan AW, Tetzlaff, Gotzsche et Al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.

CHMP Guideline on follow up of participants administered with Gene Therapy Medicinal Products (EMEA/CHMP/GTWP/60436/2007).

Cideciyan AV, Aleman TS, Boye SL et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. Proc Natl Acad Sci 2008; 105(39)15112-15117.

Cideciyan AV, Jacobsen SG, Beltran WA et Al. Human retinal gene therapy for Leber Congenital Amaurosis shows advancing retinal degeneration despite enduring visual improvement. Proc Natl Acad Sci USA, 2013, 110(6):E517-25.

Cochrane G, Lamoureux E, Keeffe J. Defining the content for a new quality of life questionnaire for students with low vision (the Impact of Vision Impairment on Children: IVI_C). Ophthalmic Epidemiol. 2008 Mar-Apr;15(2):114-20 (PubMed Abstract)

Cochrane GM, Marella M, Keeffe JE, Lamoureux EL. The Impact of Vision Impairment for Children (IVI_C): validation of a vision-specific pediatric quality-of-life questionnaire using Rasch analysis. Invest Ophthalmol Vis Sci. 2011 Mar 1;52(3):1632-40 (PubMed Abstract)

Donders F. BeitragezurpathologischenAnatomie des Auges. 2. Pigmentbildung in der Netzhaut. Arch Ophthalmol 1857; 3: 139–165 [Reference not available].

Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149-158.FDA: Guidance for Industry Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events. Nov 2006.

Feng Y, Devlin N, Shah K, Mulhern B, van Hout B. OHE Research Paper Published: 16-02-2016.

Feng Y, Devlin N, Shah K, Mulhern B, van Hout B. New Methods for Modelling EQ-5D-5L Value Sets: An Application to English Data. *Health Economics* 2018;27(1):23-38.

Guy W. ECDEU assessment manual for psychopharmacology, revised. US Department of Health, Education, and Welfare publication (ADM 76-338). Rockville: National Institute of Mental Health; 1976

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011 Dec;20(10):1727-1736.

Hong DH, Pawlyk BS, Adamian M et al. A single, abbreviated RPGR-ORF15 variant reconstitutes RPGR fu nction in vivo. Invest Ophthalmol Vis Sci 2005; 46(2):435-41.

https://euroqol.org/docs/EQ-5D-Y-User-Guide.pdf Development of the EQ-5D-Y: a child-friendly version of the EQ-5D
https://euroqol.org/docs/EQ-5D-5L-User-Guide.pdf

Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005 Sep;140(3):509-16.

Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013 Sep;22(7):1717-1727.

Lamoureux EL, Pallant JF, Pesudovs K, Hassell JB, Keeffe JE. The Impact of Vision Impairment Questionnaire: an evaluation of its measurement properties using Rasch analysis. Investigative Ophthalmology & Visual Science. 2006 Nov; 47(11):4732-41 (Full Text Article)

Lamoureux, E. L. *et al.* The impact of vision impairment questionnaire: an assessment of its domain structure using confirmatory factor analysis and rasch analysis. *Invest Ophthalmol Vis Sci* **48**, 1001-1006, doi:10.1167/iovs.06-0361 (2007).

Maguire AM, Simonelli F, Pierce EA et al. Safety and efficacy of gene transfer for Leber congenital amaurosis. N Engl J Med 2008; 358(21):2240-8.

Manno CS, Pierce GF, Arruda VR et Al. Successful transduction of liver in haemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nat Med, 2006, 12(3):342-7.

Oppe M, Devlin NJ, van HB, Krabbe PF, de CF. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. *Value in Health.* 2014;17(4):445-453.

Owsley C, McGwin Jr. G, Scilley K and Kallies K. Development of a Questionnaire to Assess Vision Problems under Low Luminance in Age-Related Maculopathy. IOVS 2006 Feb;47 (2) 528-535.

Pawlyk B, Adamian M, Sun X, Bulgakov O, Shu X, Smith A, Berson E, Ali R, Khani S, Wright A, Sandberg A, and Li T, Photoreceptor Rescue by an Abbreviated Human *RPGR* Gene in a Murine Model of X-linked Retinitis Pigmentosa*Gene Ther.* 2016 Feb; 23 (2): 196–204.

Ramos-Goñi JM, Craig BM, Oppe M, van Hout BA. EuroQol Working Paper. *Health Policy* 1996;37(1):53-72.

Ramos-Goni JM, Pinto-Prades JL, Oppe M, Cabases JM, Serrano-Aguilar P, Rivero-Arias O. Valuation and Modeling of EQ-5D-5L Health States Using a Hybrid Approach. *Med Care* 2017;55(7):e51-e58.

Ramos-Goñi JM, Oppe M, Slaap B, Busschbach JJ, Stolk EA. Quality Control Process for EQ-5D-5L Valuation Studies. *Value in Health* 2017;20(3):466-473.

Ravens-Sieberer U, Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, Egmar AC, Gusi N, Herdman M, J. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. Qual Life Res 2010;9(6):887-897.

Stieger K, Colle MA, Dubreil L et Al. Subretinal delivery of recombinant AAV serotype 8 vector in dogs results in gene transfer to neurons in the brain. MolTher, 2008, 16(5):916-23.

Tee JJ, Smith AJ, Hardcastle AJ et Al. RPGR-associated retinopathy: clinical features, molecular genetics, animal models and therapeutic options. Br J Ophthalmol. 2016 Aug; 100(8): 1022-7.

Stolk E, Ludwig K, Rand K, Van Hout B, Ramos-Goni JM. Overview, Update, and Lessons Learned From the International EQ-5D-5L Valuation Work: Version 2 of the EQ-5D-5L Valuation Protocol. *Value in Health* 2019;22(1):23-30.

van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;15(5):708-715.

Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, Egmar AC, Greiner W, Gusi N, Herdman M, Jelsma J. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res* 2010;19(6):875-886.