HORIZON: A PHASE II, OPEN-LABEL, OUTCOMES-ASSESSOR MASKED, MULTICENTRE, RANDOMISED, CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TWO DOSES OF GT005 ADMINISTERED AS A SINGLE SUBRETINAL INJECTION IN SUBJECTS WITH GEOGRAPHIC ATROPHY SECONDARY TO DRY AGE-RELATED MACULAR DEGENERATION

STUDY PROTOCOL

STUDY NUMBER:	GT005-03/ NCT04566445
VERSION:	5.0
DATE:	15 Sep 2022
SUPERSEDED VERSION/DATE:	4.0/04 Jan 2022
PRODUCT NAME/CODE:	GT005 A RECOMBINANT, NON-REPLICATING ADENO-ASSOCIATED VIRAL VECTOR SEROTYPE 2 (AAV2) EXPRESSING HUMAN COMPLEMENT FACTOR I
EudraCT NUMBER:	2020-002431-30
SPONSOR	GYROSCOPE THERAPEUTICS ROLLING STOCK YARD, 188 YORK WAY, LONDON, N7 9AS UNITED KINGDOM

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AAV	Adeno-associated virus
AAV2	Adeno-associated virus serotype 2
[redacted]	[redacted]
[redacted]	[redacted]
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
AMD	Age-related macular degeneration
AREDS	Age-related eye disease study
ATA	Anti-transgene antibodies
BCVA	Best corrected visual acuity
BSS	Balanced salt solution
C3	Complement component 3
CFB / CFB	Complement factor B (*Gene* / PROTEIN)
CFH / CFH	Complement factor H (*Gene* / PROTEIN)
CFI / CFI	Complement factor I (*Gene* / PROTEIN)
CFP	Colour fundus photography
CFR	Code of Federal Regulations
CMO	Cystoid macular oedema
CNV	Choroidal neovascular AMD
CRC	Central Reading Centre
CRO	Clinical Research Organisation
CSR	Clinical study report
DBL	Database lock
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EIU	Exposure in utero
EoS	End of study
ETDRS	Early treatment diabetic retinopathy study scale
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FAS	Full analysis set
FDA	Food and Drug Administration
FRI	Functional reading independence
GA	Geographic atrophy
GAT	Goldmann applanation tonometry
GCP	Good Clinical Practice
HEK	Human embryonic kidney
IB	Investigator's Brochure
ICF	Informed Concent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

Abbreviation	Definition
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive response technology
ISC	Independent Statistics Centre
LLD	Low luminance difference
LLVA	Low luminance visual acuity
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures analysis
MNRead	Minnesota low-vision reading (test)
NA	Not applicable
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography-angiography
OR	Odds ratio
PRL	Preferred Retinal Locus
PSA	Prostate-specific antigen
RPE	Retinal pigment epithelium
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SUSAR	Suspected unexpected serious adverse reactions
Tel	Telephone
V	Visit
VFQ	Visual function questionnaire
Vg	Vector genomes

PROTOCOL SIGNATURES

Investigator Agreement and Signature:

I, the undersigned, have read and understood the GT005-03 (HORIZON) protocol and am aware of my responsibilities as an Investigator. I agree to conduct the study in accordance with this protocol and any subsequent amendments, the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and the laws and regulations of the country in which the study is being conducted.

NAME: _____ SIGNATURE: _____

TITLE: _____ DATE: _____

INSTITUTION: _____

Sponsor's representative signature:

DocuSigned by:
[redacted]

NAME: Dr [redacted] SIGNATURE: _____

TITLE: [redacted] DATE: 15-Sep-2022

AMENDMENT HISTORY

Protocol Version	Change	Justification
Version 1.0, 04 May 2020 (Initial)	Not applicable (NA)	NA
Version 2.0, 19 Nov 2020 (Amendment 1)	Study period extended to 2 years with the addition of Weeks 72 and 96.	• The study period has been extended to 2 years to enable the capture of longer term treatment effect and durability of outcomes.
	Revision of objectives to include the additional Week 72 and 96 timepoints The addition of secondary objective: The change from baseline to Week 72 and Week 96 in geographic atrophy (GA) area as measured by fundus autofluorescence (FAF).	• Added due to extension of the study to 2 years.
	Reference to Dose 1 and 2 removed to include vector genome along with mid and high doses added for clarification to sites.	• Investigative sites involved across the clinical GT005 program are familiar with low [redacted], medium [redacted] and high doses [redacted]) and therefore edits have been made..
	Inclusion/Exclusion Criterion	• Inclusion criterion 3 language has been clarified for requirement of age-related macular degeneration (AMD) in contralateral eye • Inclusion criterion 6 has been broadened to best corrected visual acuity (BCVA) of 24 letters (6/95 and 20/320 Snellen acuity equivalent) to evaluate the treatment effect of subjects with worse-seeing vision. • Inclusion criterion 7a revised to to include an evidence-based approach to enrolment of subjects into the study. • Inclusion criterion 9 has been clarified to include further guidance relating to pregnancy testing. • Removal of exclusion criteria 1b as inclusion criteria confirms eligible variants and this text is not needed. • New exclusion criterion 5 has been added to provide clarification of prior intraocular surgery before screening. • [redacted] • Exclusion criterion 13 updated to broaden the malignancies/cancer types excluded from the study.
	Randomisation to either eye (if both eligible) removed	• The eye with worse visual acuity will be selected, if both eyes are eligible to help safeguard vision in the better seeing eye.
	Corrected the imaging modality for retinal anatomical measures	• Updated terminology to multimodal imaging as colour fundus photography (CFP) is not the only imaging modality used to measure retinal anatomical measurements

Protocol Version	Change	Justification
	Revised text for unused or expired GT005 product	• Correction of discrepant text in the protocol.
	Removal of Preferred Retinal Locus (PRL) identification in the Schedule of assessments	• The revised retinotomy location will not encroach on the PRL and therefore the requirement to identify the PRL has been removed.
	[redacted]	[redacted]
	[redacted]	• [redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Inclusion of fluorescein angiography (FA) assessment	• FA included as an assessment to verify subjects do not have choroidal neovascular AMD (CNV) at baseline or conversion to CNV during the study. • Addition that all potential FAs to be sent to CRC.
	Additional optical coherence tomography-angiography (OCT-A)	• OCT-A additional imaging added, if required, for CNV conversion.
	Clarification of OCT modalities	• The differing OCT modalities have been clarified: OCT-A (for monitoring CNV conversion), OCT macula [redacted]provide clarity to investigational sites and to add further time points if required by the Investigator to detect any safety changes on the retina, i.e. conversion to CNV, any other safety-related changes.
	Genotyping Informed Consent Form (ICF)	• Genotyping ICF included.
	Pre-surgical checks	• Clarification of the pre-surgical ophthalmic examination.
	Volume of blood (annual) altered to account for the study extension to 2 years and inclusion of Week 72 and 96 visits	• Study extension as presented in the rationale above.
	Adverse event (AE) reporting language	• Safety reporting requirements updated to collect all AEs from date of consent.
	Protocol deviations and exceptions	• Clarification of handling of protocol deviations, in response to Medicines and Healthcare Producs Regulatory Agency grounds for non-acceptance.
	Throughout the protocol	• Administrative inconsistences removed and language clarified. As these are minor revisions, they have not been summarised.
Version 3.0, 03 JUN 2021 (Amendment 2)	Inclusion/Exclusion Criterion	• Inclusion critierion 6 and exclusion criterion 1 altered to allow inclusion of patients with CNV/wet AMD in fellow eye.

Protocol Version	Change	Justification
	Corrected the imaging modality for retinal anatomical measures	• Clarification of CNV assessment with OCT, OCT-A, or FA and added text to refer to the imaging manual.
	Clarification of OCT-A certification	• Removal of erroneous text stating OCT-A certification is not required.
	Study drug distribution site language updated	• Updated text to clarify that Investigational Medicinal Product (IMP) will be despatched directly to sites from an approved local/regional distribution vendor.
	[redacted]	• [redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Administrative changes	• Correction of text related to causality assessment of adverse events associated with surgical procedures rather than study procedures. • Correction of document name for justification and definition of the serum complement factor I (CFI) threshold. • Sponsor address updated.
Version 4.0, 04 JAN 2022 (Amendment 3)	Inclusion/Exclusion Criterion	[redacted] • Inclusion criterion 8 updated to include genetic requirements for 8a. Stage 1 only. In 8b, Stage 2, subjects will not require a genotyping subgroup classification to enter into the study, as all genetic variants will be allowed in Stage 2. [redacted]

Protocol Version	Change	Justification
	Study design Figure 1 clarification	• Clarified that enrolment at Stage 1 will be complete first before enrolling Stage 2 subjects.
	Randomisation of study eye	• Provided clarification on the requirements for randomisation of the study eye in Stage 1 and 2. [redacted] • Clarification that subjects who have foveal or non-foveal GA with a CFI rare variant genotype associated with low or normal serum CFI may be enrolled in Stage 2.
	Increased total number of subjects	• Emerging evidence has suggested that complement mediating therapies may have a greater effect in subjects with non-foveal (extrafoveal) GA, [redacted]
	Number of investigative sites	• Increased the number of global sites to approximately 90 to support Stage 2 recruitment in subjects with non-foveal GA.
	Clarification of bleb number	• Correction of an inconsistency between the protocol and surgical manual to provide further clarity on the use of more than 1 bleb for the delivery of GT005.
	GT005 deferral guidance	• Clarified that in the event GT005 dosing was deferred during surgery, the time from screening may be extended up to 16-weeks. • Clarified that if the time from screening is extended past 12 weeks, in case of GT005 deferral, FAFs should be repeated in addition to the standard ophthalmic exam, haematology/biochemistry and BCVA or low luminance visual acuity (LLVA).
	Rescreening guidance ***within*** 8 weeks and ***outside*** of 8 weeks	• Provided clarification that if a subject is rescreened within the 8-week screening period, the site staff needs to repeat only the standard ophthalmic exam and visual acuity (BCVA and LLVA) assessment provided all other original results were acceptable. • Further, if a subject is rescreened outside of the 8-week screening period, all screening assessments should be repeated except for genotyping and serum CFI.
	Additional safety assessment with FAF at Week 5	• Included an additional safety assessment using FAF at Week 5, post GT005 delivery.
	Statistical analysis	• Clarified when data readouts will be made during the study given the new increase in the number of subjects.
	Vital signs	• Clarified that the blood pressure assessment may be performed in either arm in line with standard clinical practice.

Protocol Version	Change	Justification
	Throughout the protocol	[redacted] • Administrative inconsistences removed and language clarified. As these are minor revisions, they have not been summarised.
Version 5.0, 15 SEP 2022 (Amendment 4.0)	Updated primary endpoint read-out timepoint from Week 48 to Week 72	• Updated the primary endpoint read-out to Week 72 as this is considered the most appropriate timepoint to evaluate the treatment effect of GT005, since the clinical effect size is hypothesised to be linked to the exposure to higher CFI levels and thus may increase over time beyond Week 48, based upon preliminary data on expression kinetics of the CFI transgene product from our Phase I/II FOCUS study.
	Secondary endpoints [redacted]	• The study endpoints have been reviewed and the opportunity taken to rationalise the number of secondary endpoints currently listed. [redacted]
	Updates to secondary and [redacted] endpoints to be reported 'through Week 96.	• Clarified the analysis timepoints for secondary and [redacted] endpoints.
	Updates to the Statistical Methods	• Change in the primary endpoint timepoint to Week 72 from Week 48. • The following sections were expanded/added: Sample size determination, [redacted] readout timing, analysis populations. More information and detail relating to the planned statistical analysis has been added to the protocol to provide evidence for the statistical integrity and robustness of the study design. • Removed height, weight and body mass index from the planned analyses in the demographics section under Section 9.0 Statistical Methods as they are not captured in the study database.
	Clarification under the Surgical Procedure of the synopsis and Section 5.4: Dosing and Administration	• Subretinal GT005 dosing will occur across multiple administration blebs. The text regarding the subretinal bleb dosing procedure for GT005 was further clarified to better align with the Surgical Manual.
	Updated 7.4.2 Adverse Events and footnote 11 to clarify that any additional safety assessments may be collected to follow up on AEs (previously the text erroneously referenced imaging tests only)	• In order to appropriately protect subjects' safety in the study it was always intended for Investigators to have the ability to perform any additional safety tests at their clinical discretion to evaluate/monitor AEs. Accordingly, the text has been updated to reflect this original intent.

Protocol Version	Change	Justification
	[redacted]	• [redacted]
	Updated recent information under 'Risks associated with GT005.	• This section has been aligned with the current version of the Investigator's Brochure (IB).
	[redacted]	[redacted]
	Updated guidance on the timing of cataract surgery during the study under Section 1.6.1.2 Risks Associated with the Surgical and Study Procedures	• If required, cataract surgery should occur at least 4 weeks before the Week 72 visit (instead of the previous Week 48 visit). This change aligns with the revised timing of the primary endpoint of the study.
	Updates to Study Rationale	• The study rationale has been updated to include preclinical data that was originally missing from the protocol. [redacted]
	Updates to Dose Rationale	• Under Dose rationale synopsis and Section 1.55, clarified that the doses in this study, are selected to optimise the ability to demonstrate a therapeutic effect and identify an effective dose. This change was made to further clarify that a suitable dose can be selected based on the data obtained from this study for the next study.
	Clarify overall study population	• Clarified that the overall population in HORIZON (N=250) will include [redacted] foveal and [redacted] non-foveal subjects, reflective of the expected proportions of the overall population in Section 3.1 Study Overview and Section 1.5.4 Non-foveal GA. [redacted]
	Updates to Section 1.4 Clinical Studies	• Removed outdated clinical data text relating to the Phase I/II FOCUS study in the protocol since all updated clinical data are listed in the IB. The protocol already makes reference to refer to the IB, for further information.

Protocol Version	Change	Justification
	Updates to Section 3.1 Study Overview, Section 3.4.1 Masking, and Section 5.5 Measures to Minimise Bias	• Definitions of fully-masked and dose-masked to reflect the definition of masking in other clinical and regulatory documentation. No change in masking status for the study has been implemented. • Updated the text regarding [redacted] to reflect the multimodal assessment that is performed
	Administrative/formatting changes throughout	• For general document improvement, providing further clarity where necessary and following input from sites/regulators and other stakeholders. ensuring consistency, addressing inadvertent formatting and typographical errors from the last version • Administrative inconsistences removed and language clarified.

Abbreviations: AE=adverse event; AESI= adverse event of special interest; AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CNV=choroidal neovascular AMD, CRC=central reading centre; FA=fluorescein angiography; FAF=fundus autofluorescence; GA=geographic atrophy; IB=Investigational Brochure; ICF=informed consent form; IMP=investigational medical product; LLVA= low luminance visual acuity; NA=not applicable; OCT=optical coherence tomography; OCT-A=optical coherence tomography-angiography; PRL=preferred retinal location; RPE=retinal pigment epithelium.

COMPLIANCE STATEMENT

This study will be conducted in compliance with Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), informed consent regulations, the Declaration of Helsinki, ICH GCP Guidelines, and Food and Drug Administration (FDA), 21 Code of Federal Regulations (CFR) Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerised systems used in clinical trials. In addition, this study will adhere to all local regulatory requirements.

Any episode of noncompliance will be documented.

PROTOCOL SYNOPSIS

SPONSOR:

Gyroscope Therapeutics

INVESTIGATIONAL MEDICINAL PRODUCT:

GT005: A recombinant non-replicating adeno-associated viral vector derived from wild-type adeno-associated virus serotype 2 (AAV2). The expression cassette contains deoxyribonucleic acid encoding for human complement factor I (CFI).

TITLE:

HORIZON: A Phase II, open-label, outcomes-assessor masked, multicentre, randomised, controlled study to evaluate the safety and efficacy of two doses of GT005 administered as a single subretinal injection in subjects with geographic atrophy secondary to dry age-related macular degeneration.

PROTOCOL NO:

GT005-03 (HORIZON).

INDICATION:

GT005 is under development for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

INVESTIGATOR STUDY SITES:

Approximately 90 investigational sites will take part. Designated sites will perform screening and subretinal surgery for subjects allocated to GT005, and post-operative follow-up visits.

STUDY PERIOD:

Subject participation consists of a screening period of up to 8 weeks and a 96-week study period, for a total of 104 weeks.

STUDY RATIONALE:

AMD is the most common cause of blindness among the elderly in the industrialised world [Jonasson 2014], affecting approximately 36 to 40 million people globally [Access Economics Report 2010]. AMD is a progressive disease that results in a blurred area or blank spot in the centre of vision [NIH].

AMD is classified into early, intermediate, and advanced stages [Ferris 2013]. Advanced stage AMD includes two morphological subtypes: choroidal neovascular AMD (CNV) and GA [Chakravarthy 2010]. There are no approved therapies for GA.

Evidence has emerged which implicates chronic local inflammation and activation of the complement cascade in AMD pathogenesis [Anderson 2010]. A number of complement proteins have been identified as constituents of drusen, the hallmark extracellular deposits associated with AMD [Anderson 2010].

Rare Variant Genetic Population: Genetic studies have found AMD patients carrying rare genetic variants in *CFI* (defined by a minor allele frequency ≤1%) in combination with low CFI protein levels in blood serum, are more likely to have an increased risk of developing AMD which has progressed to the advanced stages of disease [Seddon 2013; Kavanagh 2015; Geerlings 2017].

As CFI serves as a global down-regulator of the alternative pathway [Lachmann 2016], an increase in intraocular CFI level has the potential to dampen an over-activated complement system associated with AMD, reducing the progression of the disease. [redacted]

[redacted]

The EXPLORE Phase II study is currently testing the hypothesis that supplementation of CFI via GT005 gene therapy will slow disease progression in a proportion of GA cases who harbour rare *CFI* variants associated with low serum CFI.

Broad Genetic Population: Overactivation of the complement system is also implicated in the risk of disease development across the broader dry AMD population, as shown by significant enrichment of common genetic risk factors mapping to complement proteins involved in the alternative pathway e.g. complement factor H (CFH), CFI, complement factor B (CFB), and complement component 3 (C3) [Fritsche 2013; Fritsche 2016].

The HORIZON Phase II study is designed to test whether administering CFI will be effective in down-regulating a hyperactive complement system across all GA patients and if this intervention will have a therapeutic effect on disease progression. CFI rare variant genotypes associated with normal or low serum CFI or subjects carrying an unreported *CFI* rare variant genotype that have tested to have a normal or low serum CFI will be considered for study entry. This hypothesis is postulated from the observation that CFI supplementation has the potential to normalise variation in complement activity in blood sera taken from individuals carrying different combinations of common complement risk variants [Lachman 2016].

Non-foveal GA: Recent data released on pegcetacoplan described a prespecified analysis of the primary endpoint where pegcetacoplan demonstrated a greater effect in subjects with non-foveal GA (extrafoveal lesions) at baseline [Wykoff C, AAO Abstract November 2021]. [redacted]

The HORIZON protocol will be composed of two stages: Stage 1 and Stage 2. Stage 1 of the protocol will continue to enrol the study until 180 genetically-defined subjects have randomised. Stage 2 of the protocol will enrol subjects with ***non-foveal GA (extrafoveal).*** In addition, subjects with foveal or non-foveal GA who have a CFI rare variant associated with normal or low serum CFI may also be enrolled in Stage 2, until approximately 250 subjects (approximately 70 additional subjects after Stage 1 is completed) are randomised.

[redacted]

DOSE RATIONALE:

[redacted]

OBJECTIVES:

The overall objective of the study is to evaluate the safety and efficacy (anatomical and functional visual outcomes) of two doses of GT005 in subjects with GA due to AMD.

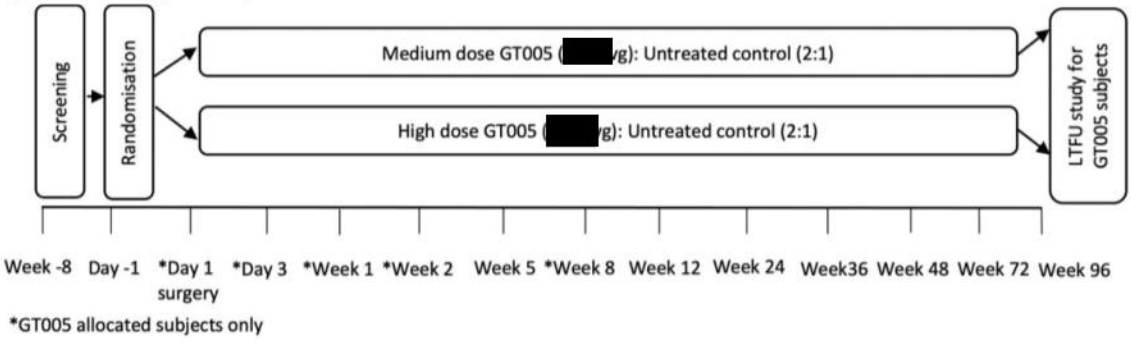
OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate the effect of GT005 vs untreated control on the progression of GA in subjects with GA due to AMD	• The change from baseline to Week 72 in GA area as measured by fundus autofluorescence (FAF)
Secondary	
• To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD	• The change from baseline through Week 96 in GA area as measured by FAF
• To evaluate the safety and tolerability of GT005	• Frequency of treatment emergent adverse events (AEs) through Week 96
• To evaluate the effect of GT005 on retinal anatomical measures	• Change in retinal morphology on multimodal imaging through Week 96
• To evaluate the effect of GT005 on functional measures	• Change in BCVA score via the early treatment for diabetic retinopathy (ETDRS) chart through Week 96 • Change in low luminance difference (LLD) via the ETDRS chart through Week 96
• To evaluate the effect of GT005 on visual function	• Change in reading performance as assessed by Minnesota low-vision reading test (MNRead) chart through Week 96 • Change in functional reading independence (FRI) index through Week 96
• To evaluate the effect of GT005 on patient-reported outcomes	• Change in quality of life measured on the visual functioning questionnaire-25 (VFQ-25) through Week 96

[redacted]

STUDY DESIGN:

This is a Phase II, open-label, outcomes-assessor masked, multicentre, randomised, controlled study designed to evaluate the safety and efficacy of two doses of GT005 administered as a single-time subretinal injection in subjects with GA secondary to dry AMD. Approximately 250 subjects, across Stage 1 and Stage 2, are planned to be randomised to one of two doses of GT005 or the untreated control group. Subjects who are screened, but not randomised, will be classified as Screen Failures and will be replaced. Subjects entered into the study must have genotyping and serum CFI evaluation performed by a Sponsor-approved laboratory, either through participation in a previous Gyroscope sponsored study or during the HORIZON screening period.

Figure 1: Study Design[1]



[1]Stage 1 subject enrolment to complete, before enrolling in Stage 2.

Following consent, subjects will undergo ophthalmic and clinical assessments to determine eligibility for inclusion in the study. On confirmation of eligibility, subjects will be randomised to one of two dose groups (medium dose [vg] or high dose [vg]). Within each dose group subjects will be allocated to GT005 or untreated control based on a 2:1 scheme [Figure 1].

Definition of Non-foveal GA:

Stage 1 will enrol subjects with GA who have foveal or non-foveal GA until 180 subjects have been randomised. Stage 2 will enrol subjects with non-foveal GA. In addition, subjects with foveal or non-foveal GA who have a CFI rare variant associated with normal or low serum CFI may also be enrolled in Stage 2, until approximately 250 subjects (approximately 70 additional subjects after Stage 1 is completed) are randomised.

Determination of Study Eye:

If both eyes are eligible; the eye with the worse visual acuity will be selected as the study eye. If visual acuity is equivalent in both eyes, the eye with the largest GA lesion size will be the study eye unless the subject (in consultation with the Surgeon) expresses an alternative preference. The study eye will be confirmed by the Surgeon.

Following randomisation, the Investigator will be informed of the subjects' allocated treatment assignment (this will only include treatment assignment to GT005 or the untreated control, and not the GT005 dose group). To minimise bias, all imaging endpoint assessments and grading will be performed at a Central Reading Centre (CRC). The Sponsor, investigators, subjects, and study personnel performing clinical assessments will remain masked to dose received for those allocated to GT005.

Subjects randomised to GT005 may undertake a visit to the surgical site between the screening and pre-surgery visit in order to meet the surgical team and discuss the procedure.

Subjects allocated to GT005 will undergo subretinal surgery for the administration of GT005. GT005 is administered as a single-time subretinal injection into the study eye, which will be performed under local anaesthesia or other anaesthetic options as considered appropriate by the Surgeon for the individual subject. Post-dosing ophthalmic and clinical assessments will be performed as described in [Table 1; Table 2]. Visits 2 to 5 will be performed for subjects randomised to GT005, as described in [Table 1].

For each subject, the study duration will be up to 8 weeks of screening (or up to 12 weeks if agreed by the Sponsor Medical Monitor), followed by a 96-week study period. Screening assessments may be conducted over several days. Subsequent follow-up visits at Weeks 12, 24, 36, 48, 72, and 96 (V6, V7, V8, V9, V10, and V11 [end of study visit]) will be conducted for both GT005 and untreated control subjects. If a subject drops out, or is withdrawn from the study, every reasonable effort will be made to complete the assessments scheduled for the early termination visit.

NUMBER OF SUBJECTS:

Approximately 250 subjects are planned to be enrolled across protocol Stage 1 and Stage 2, with subjects randomised to one of two dose groups, medium dose ([redacted] vg) and high dose ([redacted] vg). Within each dose group subjects will be allocated to the GT005 treatment group or untreated control based on a 2:1 scheme.

[redacted]

Subjects who are screened, but not randomised, will be classed as Screen Failures and will be replaced. Subjects who have been randomised will not be replaced. The reason for subject withdrawal from the study will be recorded in the electronic case report form.

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

1. Able and willing to give written informed consent
2. Age ≥55 years
3. a. **In Stage 1:** Have a clinical diagnosis of GA secondary to AMD in the study eye, as determined by the Investigator, and a diagnosis of AMD in the contralateral eye (except if the subject is monocular)
   b. **In Stage 2**: Have a clinical diagnosis of GA, secondary to AMD in the study eye, as determined by the Investigator, that is **non-foveal**, as determined by the central reading centre, or has a CFI rare variant genotype associated with normal or low serum CFI, and meets inclusion criteria 3a (e.g., foveal or non-foveal GA), and a diagnosis of AMD in the contralateral eye (except if the subject is monocular)
4. [redacted]
5. The GA lesion in the study eye must reside completely within the FAF image
6. Up to 25% of the enrolled study population are permitted to have CNV in the fellow eye, defined as either:
   - [redacted]
   - [redacted]
7. Have a BCVA of ≥24 letters (6/95 or 20/320 Snellen acuity equivalent), using ETDRS charts, in the study eye
8. Meet one of the following AMD genetic subgroup criteria, as reviewed and confirmed by the Sponsor, and be allocated to one of the following groups below:
   a. **In Stage 1**

- [redacted]
- [redacted]

- [redacted]

b. **In Stage 2:** *Genotyping is not required for study eligibility*

9. Able to attend all study visits and complete the study procedures
10. Women of child-bearing potential must have a negative pregnancy test within 2 weeks prior to randomisation or provide documentation of being surgically sterilised. A pregnancy test is not required for postmenopausal women (defined as being at least 12 consecutive months without menses) or those surgically sterilised (those having a bilateral tubal ligation/bilateral salpingectomy, bilateral tubal occlusive procedure, hysterectomy, or bilateral oophorectomy).

Exclusion Criteria:

1. Any carriers of the following genetic variants:
   - [redacted]
2. Have a history, or evidence, of CNV in the study eye
3. Presence of moderate/severe or worse non-proliferative, diabetic retinopathy in the study eye
4. Have history of vitrectomy, sub-macular surgery, or macular photocoagulation in the study eye
5. History of intraocular surgery in the study eye within 12 weeks prior to Visit 1. [redacted]
6. Have clinically significant cataract that may require surgery during the study period in the study eye
7. Presence of moderate to severe glaucomatous optic neuropathy, uncontrolled intraocular pressure (IOP), despite the use of two or more topical agents; a history of glaucoma-filtering or valve surgery is also excluded
8. Axial myopia of greater than -8 diopters in the study eye
9. Have received any investigational product for the treatment of GA within the past 6 months, or 5 half-lives (whichever is longer) other than nutritional supplements such as the age-related eye disease study formula
10. Have received a gene or cell therapy at any time
11. Have a contraindication to the protocol specified corticosteroid regimen
12. Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant
13. Active malignancy within the past 12 months, except for: appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a stable prostate-specific antigen (PSA) ≥12 months
14. Have any other significant ocular or non-ocular medical or psychiatric condition which, in the opinion of the Investigator, may either put the subject at risk or may influence the results of the study

DOSING OF THE INVESTIGATIONAL PRODUCT

The study investigational product, GT005, is supplied to the surgical site as a vial of frozen sterile liquid. GT005 is an aqueous suspension of recombinant AAV2 vector particles in [redacted]

GT005 is administered at ambient temperature as a single-time subretinal injection into the study eye of subjects allocated to GT005.

Surgical Procedure

The surgical procedure for subretinal administration of GT005 is based on standardised methodology. It is conducted by an appropriately qualified Vitreoretinal Surgeon in an operating room under local anaesthesia. Other anaesthetic options may be considered by the surgeon as appropriate for the subject. The duration of the surgery is approximately 1 hour.

Subjects allocated to treatment are injected with GT005 via a single-time administration, in a procedure involving multiple GT005 administration blebs. [redacted] The blebs usually flatten within approximately 24 hours. The detailed procedure is described in the Surgical Manual.

DURATION OF TREATMENT AND FOLLOW-UP

All subjects randomised to receive GT005 will receive a single-time subretinal injection. All subjects, those receiving GT005 and those allocated to the untreated control, will be followed for 96 weeks. After the final follow-up visit, all GT005 treated subjects will be invited to participate in a long-term follow-up study to assess safety and efficacy over time. Untreated control subjects may be eligible for future interventional studies.

REFERENCE TREATMENT:

The pooled untreated control group will provide a reference group for the two GT005 treatment groups.

STATISTICAL METHODS:

Sample Size and Statistical Power

Untreated control mean GA change at 72 weeks was assumed to be 3.0 mm^2 with standard deviation (SD) = 1.5 mm^2. The total sample size planned is approximately 250, accounting for an estimated 15% of subjects that are expected to discontinue treatment and not provide the target 72-week observation; hence power calculations are based on n=70 per treatment group (GT005 medium dose [vg], GT005 high dose [ ], pooled untreated control). [redacted]

Analysis Sets

TheThe Full Analysis Set (FAS) will include all subjects who are randomised to GT005 or untreated control. The Safety Analysis Set (SAF) will include all subjects who are randomised to GT005 or untreated control, and have at least one post-baseline observation.

Efficacy Assessments

The primary estimand will focus on the effect attributable to different doses of GT005 on GA change on FAF at Week 72 by taking into account any potential unfavourable effects of GT005. The primary

endpoint, change from baseline to Week 72 in GA area, will be estimated among treatment groups via least squares means from a mixed model repeated measures analysis (MMRM) analysis. Details of the MMRM specifications will be detailed in the statistical analysis plan (SAP). Closed MCP-Mod procedure will be applied to test each of the GT005 doses vs pooled untreated control on GA change on FAF at Week 72 while ensuring control of the family-wise type I error in the strong sense.

Categorical and binary endpoints will be summarised by counts and percentages by dose. No statistical inferential testing is planned for categorical and binary endpoints.

Safety Assessments

Safety evaluations include AEs, ophthalmic imaging and examinations, vital signs, laboratory safety (biochemistry and haematology), [redacted]

AEs will be summarised in two parts: systemic events and ocular events. For systemic events, data will be displayed according to treatment allocation (treated and untreated). Ocular events will be displayed according to treatment allocation (including GT005 dose and untreated control) and study eye (study eye and contralateral eye).

All AEs (overall, by seriousness, by severity, by relationship), including adverse events of special interest, recorded throughout the investigation will be reported following classification according to the Medical Dictionary for Regulatory Activities dictionary.

Systemic safety evaluations including vital signs, laboratory safety [redacted] will be summarised over time by dose and overall.

Ocular safety evaluations including ophthalmic examination variables (cataract grading, IOP, etc.) and BCVA scores, will be summarised in the same manner as ocular efficacy variables, dependant on data type.

[redacted]

72-Week Readouts

The analysis based on the Week 72 data will be the primary efficacy analysis for this study. The database including all Week 72 data will be locked once all enrolled patients from both Stage 1 and Stage 2 have completed the Week 72 visit or terminated the study prior to Week 72. Subjects will remain in the study and will continue their scheduled visits and assessments through the planned study duration of 96 weeks, to allow for further evaluation of efficacy and safety.

MONITORING COMMITTEES

Data Monitoring Committee

A Data Monitoring Committee (DMC) will perform safety reviews of unmasked data as well as evaluation of clinical outcomes and may recommend stopping a dose, dose adjustment, adjusting the design of the study or stopping the clinical study altogether. The DMC will be provided unmasked data by an Independent Statistics Centre (ISC) as per DMC Charter to ensure safety of the subjects. Only the DMC and ISC will be unmasked to study data during the conduct of the study.

The DMC is an independent committee that will consist of three or more individuals who cumulatively have the clinical, surgical, medical, and statistical expertise to monitor the safety of subjects in the clinical study.

No DMC member will be an Investigator in the study. Full details regarding the DMC mission and content, and DMC reviews are detailed in the DMC Charter and in the SAP.

Table 1: Schedule of Assessments: Subjects Allocated to GT005

	Local or Surgical		Surgical Site						Local or Surgical Site								Early Termination Visit
Visit Number	**1**	**Tel Call**	**2**			**Tel Call**	**3**	**Tel Call**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Visit Type/Timeframe	**Screening[1]**	**Randomisation**	**Day 1 (Dosing)** Pre-surgery[2]	**Surgery**	**Day 2** Post-surgery	**Day 3**	**Week 1**	**Week 2**	**Week 5**	**Week 8[3]**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 72**	**Week 96/EoS**	
Window	**-8 weeks**					**+1 days**	**± 3 days**	**±3 days**	**±7 days**	**+3/-7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	
Informed consent	X																
Review of eligibility	X																
Randomisation		X[4]															
Demographics	X																
Medical/surgical history	X		X														
Pregnancy test[5]	X		X														
Vital signs	X		X		X		X		X			X		X	X	X	X
Biochemistry/ haematology	X[1]								X		X	X		X	X	X	X
Serum CFI level[6]	X																
Genotyping[6]	X																
[redacted]																	
Surgery and dosing of GT005				X													
[redacted]																	
Adverse events[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge (if applicable)					X												

	Local or Surgical		Surgical Site						Local or Surgical Site								Early Termination Visit
Visit Number	**1**	**Tel Call**	**2**			**Tel Call**	**3**	**Tel Call**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Visit Type/Timeframe	**Screening[1]**	**Randomisation**	**Day 1 (Dosing)**		**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 5**	**Week 8[3]**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 72**	**Week 96/EoS**	
			Pre-surgery[2]	**Surgery**	**Post-surgery**												
Window	**-8 weeks**					**+1 days**	**± 3 days**	**±3 days**	**±7 days**	**+3/-7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	
Ophthalmic examination	X[1]				X		X		X	X	X	X	X	X	X	X	X
Pre-surgical ocular safety check			X[12]														
CFP	X								X					X	X	X	X
FAF	X[1]								X		X	X	X	X	X	X	X
OCT macula	X				X		X		X		X	X	X	X	X	X	X
[redacted]																	
OCT A	X[13]						X[14]										X[14]
Fluorescein angiography	X[13]						X[14]										X[14]
[redacted]																	
BCVA with ETDRS	X[1]						X		X	X	X	X	X	X	X	X	X
LLVA with ETDRS for LLD	X[1]										X	X	X	X	X	X	X
Visual acuity check			X[17]														
MNRead	X											X	X	X	X	X	X
VFQ-25	X											X	X	X	X	X	X
FRI index	X											X	X	X	X	X	X

Abbreviations: AAV2=adeno-associated virus serotype 2; AE=adverse event; AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CFI=complement Factor I; CFP=colour fundus photography; EoS=end of study; ETDRS=early treatment for diabetic retinopathy; FAF=fundus autofluorescence; FRI Index=functional reading independence index; LLD=low luminance difference; LLVA= low luminance visual acuity; [redacted] MNRead=Minnesota low-vision reading test; OCT=optical coherence tomography; Tel=telephone; VFQ=visual functioning questionnaire.

1. Screening assessments may be conducted over several days. The screening period may be extended up to a maximum of 12 weeks, if agreed by the Sponsor Medical Monitor. If the screening period is greater than 8 weeks, a standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA should be repeated. If a subject is rescreened ***within*** the 8-week time interval between the screening visit and dosing, only the standard ophthalmic exam and BCVA/LLVA needs to be repeated, provided the original results from the other screening assessments were acceptable for study inclusion. If a subject is rescreened ***outside*** of the 8-week screening period, all screening assessments should be repeated with the exception of genotyping and serum CFI. In the event that GT005 administration is deferred during the surgical

procedure (e.g., due to an adverse event occurring during surgery) the time from screening may be extended up to 16-weeks if agreed by the Sponsor Medical Monitor. Additionally, if the time from screening is extended past 12 weeks, in case of GT005 deferral, FAFs should be repeated in addition to the standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA.

2. Pre-surgical assessments will include any local requirements of the surgical site. Pre-surgery is defined as the time between randomisation and surgery.
3. Study assessments at Week 8 may be conducted at +3/-7 days of the study visit.
4. Randomisation will occur following confirmation of eligibility; subjects will be informed via telephone call of the randomisation outcome.
5. Only for women of child-bearing potential.
6. To be completed only if not previously performed at a Sponsor-approved laboratory.
7. [redacted].
8. [redacted]
9. [redacted]
10. [redacted]
11. AEs should be captured from signing the informed consent form. Additional assessments may be conducted, as needed, to allow for safety assessment.
12. A pre-surgical ocular safety check will be performed to verify no new adverse events that could halt surgery. Presurgical ocular safety checks should be performed as per local procedures and/or at the discretion of the Investigator assessing the subject.
13. Choroidal neovascular AMD (CNV) assessment at screening/prior to surgery may be based on history or be performed using multimodal imaging techniques, which may include OCT, optical coherence tomography-angiography (OCT-A) and/or fluorescein angiography. Further details are provided in the Central Imaging Manual.
14. OCT-A and fluorescein angiography may be performed during the study period if clinically indicated, for example, if a subject converts to wet AMD.
15. [redacted]
16. [redacted]
17. A visual acuity check using a Snellen chart (near card is permissible) must be performed on the study eye if >4 weeks have lapsed since the last BCVA with ETDRS assessment. Refer to Section 7.3.9 for further details.

Table 2: Schedule of Assessments: Subjects Allocated to Untreated Control

	Local or Surgical Site									
Visit Number	**1**	**Tel Call**	**Tel Call**	**6**	**7**	**8**	**9**	**10**	**11**	**Early Termination Visit**
Visit Type/Timeframe	**Screening[1]**	**Randomisation**	**Week 5**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 72**	**Week 96/EoS**	
Window	**-8 weeks**		**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	
Informed consent	X									
Review of eligibility	X									
Randomisation		X[2]								
Demographics	X									
Medical/surgical history	X									
Pregnancy test[3]	X									
Vital signs	X				X		X	X	X	X
Biochemistry and haematology	X[1]			X	X		X	X	X	X
Serum CFI level[4]	X									
Genotyping[4]	X									
[redacted]										
Adverse events[5]	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Ophthalmic examination	X[1]			X	X	X	X	X	X	X
CFP	X						X	X	X	X
FAF	X			X	X	X	X	X	X	X
OCT macula	X			X	X	X	X	X	X	X
OCT-A	X[6]			X[7]						X[7]
Fluorescein angiography	X[6]			X[7]						X[7]
[redacted]										
BCVA with ETDRS	X[1]			X	X	X	X	X	X	X
LLVA with ETDRS for LLD	X[1]			X	X	X	X	X	X	X
MNRead	X				X	X	X	X	X	X
VFQ-25	X				X	X	X	X	X	X
FRI index	X				X	X	X	X	X	X

Abbreviations: AE=adverse event; AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CFI=complement factor I; CFP=colour fundus photography; EoS=end of study; ETDRS=early treatment for diabetic retinopathy; FAF=fundus autofluorescence; FRI Index=functional reading independence index; LLD=low luminance difference; LLVA= Low luminance visual acuity; [redacted] MNRead=Minnesota low-vision reading test; OCT=optical coherence tomography; A; Tel=telephone; VFQ=visual functioning questionnaire.

1. Screening assessments may be conducted over several days. The screening period may be extended up to a maximum of 12 weeks, if agreed by the Sponsor Medical Monitor. If the screening period is greater than 8 weeks, a standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA should be repeated. If a subject is rescreened ***within*** the 8-week time interval between the screening visit and dosing,

only the standard ophthalmic exam and BCVA/LLVA needs to be repeated provided the original results from the other screening assessments were acceptable for study inclusion. If a subject is rescreened ***outside*** of the 8-week time interval all screening assessments should be repeated with the exception of genotyping and serum CFI.

2. Randomisation will occur upon confirmation of eligibility; subjects will be informed via telephone call of the randomisation outcome.
3. Only for women of child-bearing potential.
4. To be completed only if not previously performed at a Sponsor-approved laboratory.
5. AEs should be captured from signing the informed consent form.
6. CNV assessment at screening may be based on history or be performed using multimodal imaging techniques, which may include OCT, OCT-A, and/or fluorescein angiography. Further details are provided in the Central Imaging Manual.
7. OCT-A and/ or fluorescein angiography may be performed during the study period if clinically indicated, for example, if a subject converts to wet AMD.
8. [redacted]

1 BACKGROUND INFORMATION

A full description of the indication, investigational medicinal product (IMP), pre-clinical and clinical data available for GT005 is provided in the Investigators Brochure (IB).

1.1 Indication

Age-related macular degeneration (AMD) is the most common cause of blindness among the elderly in the industrialised world [Jonasson 2014], affecting approximately 36 to 40 million people globally [Access Economics Report 2010]. AMD is a progressive disease that results in a blurred area or blank spot in the centre of vision [NIH].

AMD is classified into early, intermediate, and late stages [Ferris 2013]. Late-stage AMD includes two morphological sub-types: choroidal neovascular AMD (CNV) and geographic atrophy (GA) [Chakravarthy 2010]. There are no approved therapies for GA.

1.2 Investigational Product

GT005 is a recombinant adeno-associated viral (AAV) vector derived from wild-type AAV serotype 2 (AAV2) [redacted] The vector genome (vg) is designed to enable cellular transduction and induce secretion of CFI via a unique subretinal delivery. GT005 is stored at ≤-60°C.

1.3 Findings from Pre-clinical Studies

[redacted]

[redacted]

[redacted]

A detailed description of the pre-clinical data is provided in the IB.

1.4 Clinical Studies

A single first-in-human, Phase I/II study, FOCUS, evaluates the safety, dose response, and efficacy of three doses (low dose, [redacted] vg; medium dose, [redacted] vg; and high-dose, [redacted] vg) of GT005 administered by subretinal injection to subjects presenting with GA due to AMD is on-going. [redacted] Safety data from the completed dose-escalation part of FOCUS supports continued development of GT005. Additional information, including preliminary data on expression kinetics of the CFI transgene product, may be found in the IB. The FOCUS study includes an expansion phase to enrol subjects with better preserved vision, who are more likely to demonstrate benefit from GT005 in an expansion cohort to evaluate the effects of GT005 in this open-label Phase I/II study.

1.5 Study Rationale

1.5.1 *The Complement Cascade*

Studies have strongly linked chronic local inflammation and the activation of the complement cascade to AMD pathogenesis [Anderson 2010; Lachmann 2016; Fritsche 2016]. A number of complement proteins have been identified as constituents of drusen, the hallmark extracellular deposits associated with AMD [Anderson 2010]. In addition to systemic production, CFI protein is expressed at low levels locally by the Müller supporting glial cells situated close to the RPE [Orozco 2020], the site of drusen formation. Amyloid-β, a major constituent of drusen, directly binds CFI, inhibiting its ability to cleave its substrate C3b to inactivated iC3b, reducing the regulation of an over-active complement system. Moreover, exposure of RPE cells to amyloid-β decreases local secretion of CFI, placing it central to the overall deregulation of complement activation in AMD [Wang 2008]. Genetic studies in advanced AMD have identified a significant enrichment of rare coding variants in the *CFI* gene (rare being defined as <1% minor allele frequency). Common variants in genes encoding complement factors involved in the alternative pathway (*complement factor H* [*CFH*], *CFI*, *complement factor B*

[*CFB*], and *complement component 3* [*C3*]) are also significantly enriched in AMD cases, but confer a much weaker risk of disease development compared to that attributed to rare variants [Fritsche 2016].

1.5.2 *Rare Variant Genetic Population*

Since CFI serves as a global down-regulator of the alternative pathway (a part of the complement system) [Lachmann 2016], an increase in intraocular CFI level has the potential to dampen an over-activated complement system associated with AMD, reducing disease progression. [redacted] Individuals who carry rare *CFI* variants that are enriched in AMD cases compared to controls and predicted to be damaging *in silico,* are also more likely to have low CFI levels in their serum. This is hypothesised to be the phenotypic consequence of a failure of protein secretion conferred by the single copy of the pathogenic genetic variant (termed 'haploinsufficiency') [Seddon 2013; Kavanagh 2015; Geerlings 2017]. Collectively these CFI haploinsufficient variants account for approximately 3% of GA cases.

EXPLORE Phase II study (starting 2020) is currently testing the hypothesis that supplementation of CFI via GT005 gene therapy will slow disease progression in a proportion of GA cases who harbour rare CFI variants associated with low serum CFI. [redacted] The HORIZON study has been updated to include 100% of the GA population (based on genetics), which includes CFI rare variant subjects associated with low serum CFI (previously only enrolled in EXPLORE) and a small proportion of subjects that carry other complement common variants, that previously had not been accounted for.

1.5.3 *Broad Genetic Population*

The HORIZON Phase II clinical study aims to assess the safety and efficacy of two doses of GT005 in a broad population of GA subjects, regardless of genotype.

The mechanism of action of GT005 is to supplement normal CFI protein in the eye to dampen macular degeneration caused by local dysregulation of complement activity. For the broader GA population, our approach is to consider more widely any effect of genetic risk variants that map to proteins in the alternative complement pathway that may influence response to GT005.

Genetic studies across familial and broad AMD have identified rare and common risk variants that map to other complement proteins in the alternative pathway, also implicating them in disease development [Fritsche 2013; Fritsche 2016]. Rare, functionally damaging variants in *CFH, CFB* and *C3* strongly predispose to AMD [Raychaudhuri 2011; Seddon 2013; Zhan 2013; Saksens 2016]. *In vitro* functional studies indicate these variants alter the protein-protein interactions necessary for normal complement regulation, leading to excessive over-activation

of the alternative pathway, which is hypothesised to manifest over decades in the degenerative processes of AMD [Raychaudhuri 2011; Seddon 2013; Zhan 2013; Yu 2014].

Other more common AMD risk variants mapping to *CFH* and *CFI* are also implicated in AMD, however their contribution to disease development is much weaker, given their overall high prevalence across healthy individuals who never develop AMD [Fritsche 2016]. However in combination, these weak risk variants may exert a larger (additive) effect on the delicate balance between complement activation and regulation [Harris 2012].

A common *CFH* AMD risk variant expected in this study is rs10922109 with an odds ratio (OR) of 0.38, and this is detected in 42.6% Caucasian AMD cases, compared to 22% in matched Caucasian controls [Fritsche 2016]. The second *CFH* AMD risk variant is rs1061170, which is a coding missense variant that changes the amino acid sequence at position 402 from a tyrosine to a histidine (p.(Tyr402His), and this is found in 58% AMD cases and 36.4% controls, with an OR of 2.38 [Fritsche 2016].

The *CFI* common AMD risk variant is rs10033900, which has a weaker OR of 1.15, and is found in 51.1% AMD cases compared to 47.7% controls. The C3 common AMD risk variant rs2230199 has a weak OR of 1.43, and found in 26.6% AMD cases compared to 20.8% controls. The protective variant at the C2/CFB/SKIV2L gene locus rs429608 is a synonym for rs116503776, which an OR of 0.57, and is found in 9% AMD cases vs 14.8% controls [Fritsche 2016].

The functional consequence of common risk variants of *CFH* have been recently shown to subtly change the delicate balance between inhibitory and activating proteins of the alternative pathway, modifying AMD risk [Laine 2007; Clark 2013; Cipriani 2020]. No data exists yet to explain a functional mechanism linking the *CFI* common risk variant and AMD development. However a similar role in tipping the alternative complement pathway regulation towards overactivation is hypothesised, where the risk variant reduces normal CFI protein expression levels by a very small magnitude, and this may be enough to predispose a carrier over their lifetime to develop AMD. Indeed, a recent study of the human plasma proteome identified a significant but very modest reduction in CFI protein levels in normal carriers of the *CFI* common risk allele [Sun 2018], and work is ongoing to explore this in more detail in AMD patients. The main functional consequence of *C3* and *C2/CFB/SKIV2L* risk variants are thought to be amino acid changes affecting C3 and CFB respectively, which adversely affect binding to other complement factor proteins, leading to hyperactivation of the alternative pathway, which contributes to disease development [(Fritsche 2016; Zhan 2013)]

[redacted]

[redacted]

During the course of the study, based on emerging data, AMD genotype subgroup enrolment capping may be introduced to achieve a minimum subgroup sample size.

1.5.4 *Non-foveal GA*

Recent data released on pegcetacoplan described a prespecified analysis of the primary endpoint where pegcetacoplan demonstrated a greater effect in subjects with non-foveal lesions at baseline. Patients with GA typically present first with non-foveal lesions, which then progress toward the fovea where central vision is impacted. With the data from two Phase III studies combined, monthly and every-other-month treatment with pegcetacoplan decreased GA lesion growth by 26% (P<0.0001) and 23% (P=0.0002), respectively, in patients with non-foveal lesions compared to pooled sham at 12 months [Wykoff C, AAO Abstract November 2021].

Based on the encouraging data for pegcetacoplan, the HORIZON protocol will be composed of two stages: Stage 1 and Stage 2. Stage 1 of the protocol will continue to enrol the study until 180 foveal and non foveal genetically-defined subjects with GA have randomised. Stage 2 of the protocol will enrol subjects with non-foveal GA (extrafoveal), and subjects with a CFI rare variant associated with normal or low serum CFI who have foveal or non-foveal GA, until approximately 250 subjects (approximately 70 additional subjects after Stage 1 is completed) are randomised. [redacted]

1.5.5 *Dose Rationale*

[redacted]

[redacted]

It has been shown that a 22 µg/mL increase in systemic CFI concentration can reduce the activity of the C3b feedback cycle of the highest risk sera to that of the lowest risk [Lachmann 2016]. [redacted]

[redacted]

1.6 Risk/Benefit Assessment

A summary of data and guidance to the Investigator is provided in the IB.

1.6.1 *Potential Risks*

The risks associated with this study can be divided into those related to the GT005 product and those related to the surgical delivery of GT005.

1.6.1.1 Risks Associated with GT005

There were no GT005-related systemic adverse effects with all doses tested in both the monkey and mouse toxicity studies. In mice, [redacted]

[redacted]

The potential risks associated with gene therapy are related to intraocular inflammation, immunogenicity, developmental risks, germ line transmission, and environmental risks as discussed below.

[redacted]

An immune response to human CFI is the most likely cause for the observed inflammatory changes in both studies. This is based upon detection of anti-CFI antibodies which correlated with incidence and severity of the findings in the retina and geniculate nucleus in monkeys. Since the generation of antibodies to human CFI is not expected following subretinal administration of GT005 in subjects, these adverse findings are likely species-specific.

[redacted]

Immunogenicity of the recombinant AAV platform has been extensively assessed in over 200 clinical studies to date [Ginn 2018], several of which were ocular gene therapy studies using subretinal injection of AAV2 vector. There have been no reported ocular toxicities observed which have been attributed to an immune response to the capsid in the treated subjects. When administered subretinally, the humoral and cellular immune response to the capsid has been limited compared to systemically administered recombinant AAVs. After repeat administration of voretigene neparvovec (Luxturna®), there was little to no change reported in antibody titres to AAV capsid when measured in systemic circulation and seemingly no correlation between presence of anti-capsid antibodies and clinical safety or efficacy [voretigene neparvovec FDA ACM 2017; Mingozzi 2013].

[redacted]

[redacted]

Raised CFI levels are expected locally in the retina without impacting the systemic complement system. While inhibition of the complement system has been associated with an increased risk of microbial infection, supplementing CFI locally does not block complement activation but merely normalises complement regulation. As such, increased susceptibility to infection would not be predicted. CFI is a normal plasma protein and acute phase protein plasma levels may rise by 150% at times of inflammation [Gleeson 2016]. Following the local injection of GT005, it is unlikely that serum levels will exceed the ranges seen in healthy individuals in various physiological states.

Reproductive and developmental abnormalities have not been reported following subretinal or systemic AAV-based gene therapy [Provost 2005]. [redacted]

Environmental risks are considered to be low, because the GT005 AAV vector is replication-deficient and has been stripped of all genetic machinery that would enable infective virions to develop. [redacted]

1.6.1.2 Risks Associated with the Surgical and Study Procedures

The surgical technique employed for this clinical study has been developed for and successfully standardised based on the Choroideremia subretinal gene therapy clinical studies [MacLaren 2014; Xue 2017]. Risk mitigations strategies have also been developed to minimise foveal or retinal stretch during vector delivery, or prevent post-surgical ocular inflammation. A careful pre-operative assessment of the retina is done as part of surgical planning, with a range of visual function tests as well as retinal imaging to determine the functional and structural integrity of the targeted retina. The risks include:

Intraocular inflammation [redacted] A transient visual loss may be observed in the first days post-surgery due to the bleb-related foveal detachment. This can be minimised by avoiding injecting into areas of retinal thinning and by not detaching the fovea, if it is deemed not necessary. Retinal detachment usually regresses over 24 hours when the subretinal fluid resolves and retinotomy self-seals. Structural recovery of the retina following iatrogenic detachment of the macula generally occurs within 1 month [Xue 2017]. Persistent retinal detachment, due to persistence of the vector bleb, can occur in less than 1 in 100 cases and may be effectively managed by retinopexy with or without appropriate intraocular tamponade. An ocular examination of the eye treated with GT005 will be performed by the Vitreoretinal Surgeon or designee on post-surgical Day 2, at Week 1 (Day 8) and Weeks 5, 12, 24, 36, 48, 72, and 96 to ensure adequate monitoring. Subjects will also be contacted by telephone per the schedule of assessments for the review of AEs.

Cataract formation is associated with any vitrectomy procedure and is also a risk of periocular or topical steroid use. In a published study from [Feng 2014], cataract appeared in approximately 40% of subjects following pars plana vitrectomy and resulted in a cataract extraction over the following 2 years. In publicly available safety data, voretigene neparvovec (Luxturna®), a subretinally delivered AAV2-RPE65 for the treatment of RPE65 retinal dystrophy, was administered in 81 eyes and of those, 11 eyes (14%) from seven subjects had documented progression of existing cataract or formation of new cataract. Three subjects had their cataract successfully extracted and other cataract cases did not receive elective extraction procedures [voretigene neparvovec FDA ACM 2017]. The study population of advanced AMD subjects is expected to have a mean age above or equal to 60 years and therefore may have already undergone a cataract extraction. At screening, subjects participating in this HORIZON GT005 study and assessed as likely to require cataract surgery during the study period will be not be included, or will be offered the option of removing their cataract before being (re)screened in the study. Participants who develop cataracts during the study may undergo cataract surgery if deemed clinically necessary; if surgery is performed, it should be carried out at least 4 weeks before Week 72 visit.

IOP elevation [redacted] publicly available safety data, voretigene neparvovec (Luxturna®), elevation in IOP was reported in eight of 81 eyes treated (10%). Subjects enrolled in the HORIZON study will have IOP checked at every hospital visit to ensure adequate monitoring and therapies will be prescribed as needed based on local standard. At screening, subjects with moderate or advanced glaucoma will not be included in the study to minimise this risk.

Worsening of vision is an uncommon risk associated with the surgical procedure or vitreous tap and could be the result of endophthalmitis or retinal damage. Risk is mitigated by design of the surgical procedure, surgeon qualification standards and close monitoring post-operatively.

1.6.2 Potential Benefits

AMD is a progressive degenerative disease and is the most common cause of blindness among the elderly in the western world. Supplementing AMD subjects with human CFI (a down regulator of the complement system) has the potential to dampen an over-activated complement system associated with AMD and slow down disease progression. Using AAV2 vector-based CFI gene transfer (GT005) could have the potential to provide sustained expression of human CFI in subjects' eyes with one single-time injection. The true impact of GT005 can only be

hypothesised as participants may not receive any clinical benefit. Given the degenerative nature of AMD, it is not expected to see any gain in visual acuity as once RPE and photoreceptors have degenerated, the function is definitively lost in the atrophic area. The potential benefit would be to slow down macular atrophy extension and ultimately prevent future vision loss.

1.6.3 Risk Benefit Analysis

GT005 is currently being evaluated in an ongoing Phase I/II clinical study and therefore the potential risks are based on clinical data from an ongoing dose-escalation safety study, pre-clinical data, and available scientific knowledge on other ophthalmic AAV2 gene therapy products (e.g. voretigene neparvovec [Luxturna®]). The main product-related risks are the generation of cellular and/or humoral immune responses to the AAV capsid. ATA immune responses seen in toxicology studies are considered to be species-specific and are therefore not expected in subjects with lifelong CFI exposure.

The surgical technique for the subretinal delivery of gene therapy builds upon established subretinal procedures such as subretinal tissue plasminogen activator injection and has been standardised for the Choroideremia gene therapy clinical studies [MacLaren 2014; Xue 2017]. Careful pre-dosing assessments and perioperative measures are planned to minimise and monitor any complication(s).

The risk to subjects exposed to GT005 is therefore considered to be low and upon careful evaluation of the potential benefits afforded by the development of such a treatment, the risk/benefit ratio of GT005 in the study population is favourable.

2 STUDY OBJECTIVES AND ENDPOINTS

The overall objectives of the study are to evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD.

OBJECTIVES	ENDPOINTS
Primary	
• To demonstrate the effect of GT005 vs untreated control on the progression of GA in subjects with GA due to AMD	• The change from baseline to Week 72 in GA area over time as measured by FAF
Secondary	
• To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD	• The change from baseline through Week 96 in GA area as measured by FAF
• To evaluate the safety and tolerability of GT005	• Frequency of treatment emergent AE through Week 96
• To evaluate the effect of GT005 on retinal anatomical measures	• Change in retinal morphology on multimodal imaging through Week 96
• To evaluate the effect of GT005 on functional measures	• Change in best corrected visual acuity (BCVA) Score via the early treatment for diabetic retinopathy (ETDRS) chart through Week 96 • Change in low luminance difference (LLD) via the ETDRS chart through Week 96
• To evaluate the effect of GT005 on visual function	• Change in reading performance as assessed by Minnesota low-vision reading test (MNRead) chart through Week 96 • Change in functional reading independence (FRI) index through Week 96
• To evaluate the effect of GT005 on patient-reported outcomes	• Change in quality of life measured on the visual function questionnaire-25 (VFQ-25) through Week 96

[redacted]

3 STUDY DESIGN

3.1 Study Overview

This is a Phase II, open-label, outcomes-assessor masked, untreated-control, multicentre, randomised controlled study to evaluate the safety and efficacy of two doses of GT005 administered as a single-time subretinal injection in subjects with GA secondary to dry AMD.

Approximately 250 subjects are planned to be randomised to one of two doses of GT005 or the untreated control group (2:1). Subjects who are screened, but not randomised, will be classed as Screen Failures and will be replaced.

Subjects entered into the study must have genotyping and serum CFI evaluation performed by a Sponsor-approved laboratory, either through participation in another Gyroscope sponsored study or during the HORIZON screening period. Data from subjects screened in another Gyroscope sponsored study at the same investigative site as HORIZON may be used to fulfil the screening and eligibility requirements for this study. This is only permissible if the screening data is collected within the screening period specified in the clinical protocol. Following consent, subjects will undergo ophthalmic and clinical assessments to determine eligibility for inclusion in the study. Should subjects fail to meet the eligibility for HORIZON, they will be classed as Screen Failures for this study and may be considered for entry into another Gyroscope sponsored study.

[redacted]

Subjects will be randomised and stratified in accordance with the randomisation stratification guidance in Protocol Section 3.4.2 and the Determination of Study Eye guidance in Protocol Section 3.4.3.

Following randomisation, the Investigator will be informed of the subjects' allocated treatment assignment (this will only include treatment assignment to GT005 or the untreated control). To minimise bias, all imaging endpoint assessments and grading will be performed at a Central Reading Centre (CRC). All imaging efficacy assessments are to be performed in a fully masked fashion (individuals are unaware of a specific participant's treatment assignment). Imaging paramters related to bleb will be designated to a separate dose-masked (individuals are unaware of a specific participant's dose assignment) reader at the CRC. The Sponsor, investigators,

subjects, and study personnel performing clinical assessments will remain masked to dose received for those allocated to GT005.

Subjects randomised to GT005 may undertake a visit to the surgical site between the screening and pre-surgery visit in order to meet the surgical team and discuss the procedure.

[redacted]

For each subject, the study duration will be up to 8 weeks of screening (or up to 12 weeks if agreed by the Sponsor Medical Monitor) followed by a 96-week study period. Screening assessments may be conducted over several days. AEs should be captured from date of informed consent. Furthermore, all subjects will be assessed for the occurrence of AEs at each visit and will undergo functional visual and retinal imaging and anatomical assessments and biological sampling as per the schedule of assessments [Table 1; Table 2].

Subsequent follow-up visits at Weeks 12, 24, 36, 48, 72, and 96 (V6, V7, V8, V9, V10, and V11) will be conducted for both GT005 and untreated control subjects. Visit 11 will be Week 96 and end of study visit. If a subject drops out, or is withdrawn from the study, every reasonable effort will be made to complete the assessments scheduled for the Early Termination Visit.

3.2 Dose Selection

GT005 is a recombinant, non-replicating AAV2 expressing human CFI.

[redacted]

3.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) will perform safety reviews of unmasked data as well as evaluation of clinical outcomes and may recommend stopping a dose, dose adjustment, adjusting the design of the study or stopping the clinical study altogether. The DMC will be provided unmasked data by an Independent Statistics Centre (ISC) as per DMC Charter to ensure safety of the subjects. Only the DMC and ISC will be unmasked to study data during the conduct of the study.

The DMC is an independent committee that will consist of three or more individuals who cumulatively have the clinical, surgical, medical, and statistical expertise to monitor the safety of subjects in the clinical study.

No DMC member will be an Investigator in the study. Full details regarding the DMC mission and content, and DMC reviews are detailed in the DMC Charter and in the Statistical Analysis Plan (SAP).

3.4 Randomisation and Masking

3.4.1 *Masking*

This is an open-label, outcomes-assessor masked study. Given a double-masked design is not feasible (i.e. treatment involves a surgical procedure) the Sponsor, Investigator, the site personnel and the subject will be unmasked to GT005 treatment or untreated control allocation (i.e. open-label). However, the Sponsor, Investigator, site personnel and the subject will remain masked to the GT005 dose group assigned.

The Sponsor will be unmasked once the Week 72 database lock is reached. However, masking to the doses will be maintained at the site level (subjects, masked site personnel and masked monitors) until the end of the study.

To minimise bias, all imaging endpoint assessments and grading will be performed at a CRC. All imaging efficacy assessments are to be performed in a fully masked fashion. Imaging parameters related to bleb will be designated to a separate dose-masked reader at the CRC.

Unmasked study site personnel will be assigned the responsibility of preparing the GT005 solution for administration, which for the medium dose ([redacted] vg) will involve a dilution. GT005 preparation will take place in a designated area remote from the investigative team to preserve masking of the treatment group. Personnel delegated to prepare GT005 will not be involved in any other aspect of the study (i.e. safety/efficacy assessments, surgical procedure).

3.4.2 *Randomisation/Stratification*

Stage 1 will enrol subjects with GA who have foveal or non-foveal GA (extrafoveal) until 180 subjects have been randomised. Stage 2 will enrol only subjects with non-foveal GA, and subjects with CFI rare variants associated with normal or low serum CFI who have foveal or non-foveal GA, until approximately 70 additional subjects are randomised (total N = approximately 250).

[redacted]

[redacted]

A treatment assignment will be allocated by interactive response technology (IRT) (additional details will be found in the IRT reference manual provided to each site). Authorised personnel at investigative sites will use the IRT system to randomise subjects. IRT will assign subjects to a treatment code number based on a pre-defined randomisation list that will be created by a statistician who is independent from the study. In case of technical randomisation queries, a 24-hour helpline is available as detailed in the IRT reference manual.

Upon randomisation, subjects will be immediately informed of allocation. For subjects allocated to the untreated control arm, Day 1 will be defined as the day following randomisation for the calculation of Week 5 to 96 visits.

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

3.4.3 *Determination of Study Eye*

If both eyes are eligible; the eye with the worse visual acuity will be selected as the study eye. If visual acuity is equivalent in both eyes, the eye with the largest GA lesion size will be the study eye unless the subject (in consultation with the Surgeon) expresses an alternative preference. The study eye will be confirmed by the Vitreoretinal Surgeon. [redacted]

[redacted]

3.4.4 *Breaking the Randomisation Code*

IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unmasking of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unmasking is warranted, the Investigator should make every effort to contact the Sponsor Medical Monitor prior to unmasking the subject's treatment assignment, unless this could delay emergency treatment of the subject. To break the blind, the Investigator may open the provided emergency envelope to reveal the code to be entered in IRT to unmask the subject's treatment.

The integrity of the emergency envelope(s) should be routinely checked by the study monitors. The emergency envelope(s) must be collected from the investigative site prior to study close-out, ensuring they are intact.

3.5 Duration of Subject Participation

All subjects randomised to GT005 will receive a single-time subretinal injection.

All subjects, those allocated to GT005 or untreated control, will be followed for 96 weeks. After the final follow-up visit, all GT005-treated subjects will be invited to participate in an extension study (ORACLE) for long-term follow-up to assess safety and efficacy. Subjects allocated to untreated control may be eligible for other interventional GT005 studies.

3.6 Early Study Termination

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events (SAEs) and adverse events of special interest (AESI) will be reviewed as they are reported from the study centre to identify safety concerns. The DMC will review unmasked data and may recommend stopping a dose, dose adjustment, adjusting the design of the study, or stopping the clinical study altogether. The study may be terminated by the Sponsor at any time. Reasons for termination may include but are not limited to, the following:

- The incidence or severity of an AE or safety profile of GT005 in this or other studies indicates a potential health hazard for study subjects
- Insufficient subject enrolment or any information becoming available during the study that substantially changes the expected benefit risk profile of GT005

3.7 End of Study Definition

The end of the study will be defined as the last visit by the last subject.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects entered into the study must meet the following criteria:

1. Able and willing to give written informed consent
2. Age ≥55 years
3. [redacted]
4. [redacted]
5. The GA lesion in the study eye must reside completely within the FAF image
6. Up to 25% of the enrolled study population are permitted to have CNV in the fellow eye, defined as either:
   - [redacted]
   - [redacted]
7. Have a BCVA of ≥24 letters (6/95 or 20/320 Snellen acuity equivalent), using ETDRS charts, in the study eye
8. Meet one of the following AMD genetic subgroup criteria, as reviewed and confirmed by the Sponsor, and be allocated to one of the following groups below:
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
9. Able to attend all study visits and complete the study procedures
10. Women of child-bearing potential must have a negative pregnancy test within 2 weeks prior to randomisation or provide documentation of being surgically sterilised. A

pregnancy test is not required for postmenopausal women (defined as being at least 12 consecutive months without menses) or those surgically sterilised (those having a bilateral tubal ligation/bilateral salpingectomy, bilateral tubal occlusive procedure, hysterectomy, or bilateral oophorectomy).

4.2 Exclusion Criteria

Subjects will NOT be included in the study if they meet any of the following criteria:

1. Any carriers of the following genetic variants:

   [redacted]

2. Have a history, or evidence, of CNV in the study eye
3. Presence of moderate/severe or worse non-proliferative, diabetic retinopathy in the study eye
4. Have history of vitrectomy, sub-macular surgery, or macular photocoagulation in the study eye
5. History of intraocular surgery in the study eye within 12 weeks prior to Visit 1. [redacted]
6. Have clinically significant cataract that may require surgery during the study period in the study eye
7. Presence of moderate to severe glaucomatous optic neuropathy, uncontrolled IOP, despite the use of two or more topical agents; a history of glaucoma-filtering or valve surgery is also excluded
8. Axial myopia of greater than -8 diopters in the study eye
9. Have received any investigational product for the treatment of GA within the past 6 months or 5 half-lives (whichever is longer), other than nutritional supplements such as the age-related eye disease study (AREDS) formula
10. Have received a gene or cell therapy at any time
11. Have a contraindication to the protocol specified corticosteroid regimen
12. Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant
13. Active malignancy within the past 12 months, except for: appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a stable prostate-specific antigen (PSA) ≥12 months
14. Have any other significant ocular or non-ocular medical or psychiatric condition which, in the opinion of the Investigator, may either put the subject at risk or may influence the results of the study

4.3 Screen Failures and Replacements

Subjects who are screened but not randomised will be classed as Screen Failures and will be replaced. A subject can be screened twice if the reason for ineligibility is transient (e.g., a cataract requiring cataract extraction), to allow the 8-week time interval between baseline assessment of the screening visit and dosing to be maintained (or up to 12 weeks if agreed by the Sponsor Medical Monitor). If the screening period is extended past the original 8-week screening period, a standard ophthalmic exam, haematology and biochemistry, and visual acuity (BCVA and low luminance visual acuity [LLVA]) assessments should be repeated.
If a subject is rescreened ***within*** the 8-week time interval between the screening visit and dosing, only the standard ophthalmic exam and visual acuity (BCVA and LLVA) needs to be repeated provided the original results from the other screening assessments were acceptable for study inclusion. If a subject is rescreened ***outside*** of the 8-week screening period, all screening assessments should be repeated with the exception of genotyping and serum CFI.

4.4 Randomisation Criteria

Subjects who have been randomised, will not be replaced.

All subjects enrolled must be identifiable throughout the study. The Investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

Following confirmation of eligibility for the study, subjects will be allocated to one of the dosing groups specified in Section 3.2.

4.5 Contraception

Females of child-bearing potential (not surgically sterile, 1 year post-menopausal or 2 years after amenorrhea) are required to use two methods of contraception (one of which being a barrier method) and must agree to continue to use these methods of contraception for 90 days post-dosing. Acceptable methods of contraception include barrier method with spermicide, intrauterine device, or steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method or abstinence. True abstinence is defined when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male subjects who have female partners of child-bearing potential, should, with their partner, use a barrier method in conjunction with a second method of contraception for 90 days post-dosing.

[redacted]

4.6 Discontinuation/Withdrawal Procedures

In all circumstances, subjects will be made aware of their right to refuse participation in a clinical study and are entitled to freely withdraw their informed consent, without giving reasons. Subjects should be assured that withdrawal from the study will not cause prejudice, will not result in any determinant, and will not affect treatment. In addition, refusal to give consent or withdrawal of consent to participate in research must not lead to any liability or discrimination (e.g. with regard to insurance or employment) against the person concerned.

As GT005 is a gene therapy, once surgery has taken place, subjects can withdraw from the study but cannot withdraw from treatment.

The reason for discontinuation/withdrawal of subjects must be determined by the Investigator and recorded in the subject's medical record and in the electronic case report form (eCRF). If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF. The date of withdrawal from the study must be recorded in the eCRF.

Reasons for discontinuation include but are not limited to:

- Withdrawal by subject
- Withdrawal by Investigator
- Death
- Lost to follow-up

Should a subject decide to withdraw from the study after GT005 administration, or should the Investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as specified in the early termination visit schedule [Table 1; Table 2].

All subjects participating in the clinical study will receive an alert card from the Investigator, which has been previously agreed by the Sponsor and approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB). At a minimum it will contain the name of the subject, the Investigator contact number and information regarding the medical treatment received by the subject.

Whether a subject is withdrawn from the study at their own request or based on a decision of the Investigator, follow-up should be maintained, subject to the consent of the subject.

4.7 Lost to Follow-up

Long-term safety assessment of subjects treated with a gene therapy product is a regulatory requirement and every effort will be made to continue monitoring long-term subject safety. If a subject is lost to follow-up, every effort should be made to contact the subject's Primary Care Practitioner or General Practitioner, with the subject's consent, to obtain information on the subject's status.

4.8 Long-term Follow-up

All subjects who receive treatment with GT005, including those that have withdrawn from the study for any reason, will be invited to participate in a long-term follow-up study (ORACLE) after the final follow-up visit at Week 96. Any unresolved AEs from this study will be monitored until the event has resolved, subsided or stabilised in the long-term study. If a subject does not agree to participate in the long-term follow-up study, any ongoing AEs will be followed until the event has resolved, subsided or stabilised.

5 STUDY TREATMENT

GT005 is a recombinant, non-replicating AAV2 expressing human CFI.

5.1 Acquisition and Accountability

GT005 will be supplied to the surgical site.

The Investigator, or designee (e.g. Pharmacist), will ensure that all GT005 is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements and will be dispensed by qualified staff members who have been designated as unmasked.

The designated unmasked study member(s) is (are) responsible for GT005 accountability, reconciliation, and record maintenance throughout the study. Accountability records must be maintained throughout the course of the study and these must be available for inspection by the study monitor during the study. All expired GT005 should be recorded in the accountability records and will be destroyed locally, as per local guidelines once final accountability is completed.

Instructions for the handling and preparation of GT005 are detailed in the Pharmacy Manual.

5.2 Formulation, Appearance, Packaging and Labelling

GT005 is a genetically modified organism that will be supplied to the surgical site as a vial of frozen sterile liquid. GT005 is an aqueous suspension of recombinant AAV2 vector particles in [redacted] GT005 will be labelled in accordance with Annex 13: Manufacture of Investigational Products.

[redacted]

5.3 Product Preparation, Storage, and Dispensing

GT005 post-administration measures regarding disposables are detailed in the Pharmacy Manual.

[redacted]

[redacted] GT005 should be handled as per the Pharmacy manual.

5.4 Dosing and Administration

GT005 will be assessed at two doses; medium dose ([redacted] vg) and high dose ([redacted] vg).

GT005 is administered as a single-time subretinal injection into the study eye of subjects allocated to one of the two GT005 doses. The surgical procedure for subretinal administration of GT005 is based on standardised methodology. It is conducted by an appropriately qualified Vitreoretinal Surgeon in an operating room under local anaesthesia. Other anaesthetic options may be considered by the Surgeon as appropriate for the subject. The duration of surgery is approximately 1 hour. The detailed procedure is described in the Surgical Manual.

Subjects allocated to GT005 treatment are injected with GT005 across a minimum of two separate administration blebs following the procedure below:

[redacted]

Subjects allocated to the untreated control will not receive any treatment.

5.5 Measures to Minimise Bias: Randomisation and Masking

This is an open-label, outcomes-assessor masked study. The Sponsor, Investigator, site personnel and subject will be unmasked to whether a subject has been assigned to GT005 or untreated control. However, the Sponsor, Investigator, site personnel and the subject will remain masked to the GT005 dose allocated. In order to minimise the potential impact of knowledge of treatment, the randomisation list will be kept strictly confidential, such that no aggregate statistical analyses by efficacy across the study by treatment shall be performed prior to the database lock/interim analysis (as applicable), except for those specified in the DMC charter review for the closed sessions.

Unmasked study personnel will be assigned to prepare GT005 for administration; however, they will not be involved in any other aspect of the study (i.e. safety/efficacy assessments, surgical procedure).

To minimise bias, all imaging endpoint assessments and grading will be performed at a CRC. All imaging efficacy assessments are to be performed in a fully-masked fashion. [redacted] The randomisation process is defined in Section 3.4.

Additional measures to minimise bias include standardised methodologies across participating sites, and similar visit/assessment schedule for treated/untreated subjects.

5.6 Concomitant Medication/Therapy Rescue Medication

5.6.1 *Required/Permitted Medication*

During the course of the study, subjects will be allowed to continue taking all prescribed and non-prescribed medications, unless specified in the exclusion criteria (see Section 4.2).

Prior to administering the corticosteroid therapy, investigators must refer to relevant Summary of Product Characteristics and/or label guidance for use. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Note that AREDS based supplements are permitted as no effect on progression of GA has been reported.

Concomitant medications will be checked throughout the study and any change in medication after the date on which the subject signs the informed consent should be recorded in the eCRF.

5.6.2 *Prohibited Medication*

There are no contraindicated medications for GT005 treatment. Potential subjects who previously received a gene/cell-based therapy at any time are excluded.

5.7 Treatment of Overdose of GT005

In the event of overdosing of GT005, the site personnel must document and report the error to the overseeing Investigator. In the event of inflammation, subjects should be treated with corticosteroids.

5.8 Administration Compliance

The product is delivered as a single-time administration by subretinal injection. The subretinal injection is undertaken by a qualified and trained Vitreoretinal Surgeon at a centralised surgical site. The Investigator at the surgical site is responsible for ensuring GT005 is handled in accordance with the protocol and is only administered to subjects enrolled into the study that are allocated to receive GT005 through IRT.

6 STUDY PROCEDURES

The schedule of observations and assessments during the study are summarised in [Table 1; Table 2] for subjects allocated to GT005 and subjects allocated to the untreated control, respectively. As treatment assignment will not be known until randomisation, the screening assessments listed in the schedule of assessments are the same in both tables.

Subjects enrolled at local investigational sites and randomised to GT005 may be invited to travel to a conveniently located surgical site for treatment and immediate post-operative follow-up visits only as summarised in [Table 1].

Definition of Local Site versus Surgical Site

Local investigational sites are defined as sites that are approved to participate in this clinical study, but require identified subjects to be transferred for surgery. Subject consent, screening, and post-operative follow-up visits will be conducted according to the visit schedule outlined in schedule of assessments [Table 1] and [Table 2].

Surgical sites are defined as sites that are approved to participate in this clinical study and to perform the surgical procedure as part of this clinical protocol. If a subject is screened at the surgical site, all assessments will be performed at this site.

Following successful screening and randomisation, pre- and post-surgical assessments should be performed at the surgical site for subjects randomised to GT005. Subjects will complete the remainder of assessments at the local site as per the schedule of assessments [Table 1] and [Table 2].

6.1 Study Visits

6.1.1 *Screening (Visit 1: Local or Surgical)*

Genotyping Visit

Subjects entered into the study must have genotyping and serum CFI evaluation performed by a Sponsor-approved laboratory, either through participation in another Gyroscope sponsored study, or during the HORIZON screening period. Subjects being considered for inclusion (who have not been previously genotyped in a Gyroscope sponsored study) will be required to provide a consent, agreeing to provide a sample for genetic testing or permit the analysis of an existing sample for this HORIZON protocol. Following subject consent, samples will be collected and shipped to a central laboratory for genotyping. Samples will be used for genetic testing for variants relating to AMD.

Where necessary, and to facilitate the completion of all screening assessments, Visit 1 can occur over a number of days.

Screening Assessments

A HORIZON study written informed consent must be obtained for each subject prior to any conduct of study-related procedures. The screening assessments will determine the eligibility of each subject and should be performed within 8 weeks of the planned dosing date (or up to 12 weeks if agreed by the Sponsor Medical Monitor). Refer to Protocol Section 4.3 for rescreening guidelines.

Data from subjects screened in another Gyroscope sponsored study, conducted at the same investigative site as the HORIZON study, may be used to fulfil the screening and eligibility

requirements for this study. This is only permissible if the screening data is collected within the screening period specified in the clinical protocol. Should subjects fail to meet the eligibility for HORIZON, they will be classed as Screen Failures for this study and may be considered for entry into another Gyroscope sponsored study.

The following screening assessments are required for ALL subjects:

- AEs
- Demographics
- Medical/surgical history
- Concomitant medication
- Pregnancy test (for women of child-bearing potential only)
- Vital signs
- Biochemistry and haematology[1]
- Serum CFI Level (only required if not already available from a Sponsor-approved laboratory)
- Genotyping (only required if not already available from a Sponsor-approved genetics laboratory)[2]
- [redacted]
- Ophthalmic examination
- CFP
- FAF
- OCT Macula
- CNV assessment; may be based on history or be performed using multimodal imaging techniques, which may include OCT, OCT-A and/or FA. Further details are provided in the Central Imaging Manual.
- [redacted]
- BCVA using ETDRS[1]
- LLVA using ETDRS for LLD[1]
- Reading performance (MNRead)
- Visual function questionnaire (VFQ-25)
- FRI Index

[1]The screening period may be extended up to a maximum of 12 weeks, if agreed by the Sponsor Medical Monitor. If the screening period is greater than 8 weeks, standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA should be repeated.
[2]In Stage 2, genotyping will be required for stratification of subjects into AMD subgroups (Groups 1–5).

6.1.2 *Randomisation (Telephone Call)*

Randomisation will occur upon confirmation of eligibility. The Investigator will follow the randomisation procedure (IRT), as described in Section 3.4, and inform the subject of treatment allocation (GT005 or untreated control).

For subjects randomised to the untreated control, Day 1 will be defined as the day following randomisation for the calculation of Week 5 to 96 visits.

For subjects randomised to GT005, the day of surgery is described as Day 1 in the study timeline (Section 6.1.3). The interval between randomisation and Day 1 must be sufficient to allow arrangements to be made for surgery, and to prepare the subject, as appropriate, for treatment. Randomisation therefore resides within the interval between screening and surgery, which should not exceed 8 weeks, unless agreed by the Sponsor Medical Monitor, who may approve an extension for up to a maximum of 12 weeks.

The Investigator will ask the subject if any changes have occurred since the screening visit and record in the eCRF:

- AEs
- Concomitant medication

6.1.3 *Visit 2, Day 1 (Surgical Site)*

Visit 2 will only apply to subjects randomised to GT005.

This visit will be performed at a centralised surgical site and will be split in three parts to be conducted over 2 days: pre-surgery (Day 1), surgery (Day 1) and post-surgery (Day 2).

6.1.3.1 Pre-surgery Day 1 (Surgical Site)

Pre-surgical assessments will include any local requirements of the surgical site. Pre-surgery is defined as the time between randomisation and surgery. The following assessments are required pre-surgery:

- Medical/surgical history
- Concomitant medication
- Pregnancy test (for women of child-bearing potential only)
- Vital signs
- AEs
- [redacted]
- [redacted]

- Pre-surgical ocular safety check to verify there are no new ocular AE that would halt surgery
- Snellen visual acuity (refer to Section 7.3.9)

6.1.3.2 Surgery Day 1 (Surgical Site)

Deferred GT005 Delivery

In the event the GT005 administration is deferred during the surgical procedure (e.g. due to an AE occurring during surgery) the time from screening may be extended up to 16 weeks if agreed by the Sponsor Medical Monitor. Additionally, if the time from screening is extended past 12 weeks, in case of GT005 deferral, FAFs will be repeated, in addition to standard ophthalmic examination, haematology and biochemistry, and visual acuity (BCVA and LLVA).

The following assessment are required during surgery:

- [redacted]
- AEs
- Concomitant medications
- [redacted]

The procedure for the administration of GT005 is described in Section 5.4.

6.1.4 *Post-Surgery Day 2 (Surgical Site)*

The following assessment are required post-surgery and prior to the discharge (if applicable) of the subject:

- Concomitant medication
- [redacted]
- Vital signs
- AEs
- Ophthalmic examination
- [redacted]
- OCT macula

6.1.5 *Day 3 (Telephone Call)*

Day 3 telephone call will only apply to subjects randomised to GT005.

The following information will be recorded:

- Concomitant medication
- [redacted]
- AEs

6.1.6 *Visit 3, Week 1 (Surgical Site)*

Visit 3 (Week 1) will only apply to subjects randomised to GT005.

The following assessments will be performed:

- Concomitant medication
- [redacted]
- AEs
- Vital signs
- Ophthalmic examination
- BCVA using ETDRS
- OCT macula
- [redacted]
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.7 *Week 2 (Telephone Call)*

Week 2 telephone call will only apply to subjects randomised to GT005.

The following information will be recorded:

- Concomitant medication
- [redacted]
- AEs

6.1.8 *Visit 4, Week 5 (Local or Surgical Site for GT005 Subjects/Telephone Call for Untreated Control Subjects)*

At Week 5, subjects may choose to attend a local investigative site or surgical site for clinical assessments and ophthalmic imaging, with review of images by both the Investigator and the surgeon.

Subjects allocated to untreated control will receive a telephone call to review concomitant medications and AEs.

Visit 4 (Week 5) assessments listed below will only apply to subjects randomised to GT005.

The following assessments will be performed:

- Concomitant medication
- [redacted]
- Vital signs
- AEs
- Biochemistry and haematology

- [redacted]
- Ophthalmic examination
- FAF
- OCT macula
- [redacted]
- BCVA using ETDRS
- CFP
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.9 *Visit 5, Week 8 (Local or Surgical Site)*

Visit 5 (Week 8) will only apply to subjects randomised to GT005

- Corticosteroid compliance
- AEs
- Concomitant medication
- Ophthalmic examination
- BCVA with ETDRS
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.10 *Visit 6, Week 12 (Local or Surgical Site)*

The following assessments will be performed in ALL subjects unless otherwise specified:

- Concomitant medication
- [redacted]
- AEs
- [redacted]
- Biochemistry and haematology
- [redacted]
- Ophthalmic examination
- FAF

- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.11 *Visit 7, Week 24 (Local or Surgical Site)*

The following assessments will be performed for ALL subjects unless otherwise specified:

- Concomitant medication
- Vital signs
- AEs
- Biochemistry and haematology
- [redacted]
- [redacted]
- Ophthalmic examination
- FAF
- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- Reading performance (MNRead)
- Visual function questionnaire (VFQ-25)
- FRI index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.12 *Visit 8, Week 36 (Local or Surgical Site)*

The following assessments will be performed for ALL subjects unless otherwise specified:

- Concomitant medication
- AEs
- Ophthalmic examination
- FAF
- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- Reading performance (MNRead)
- Visual function questionnaire (VFQ-25)
- FRI index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.13 *Visit 9, Week 48 (Local or Surgical Site)*

The following assessments will be performed for ALL subjects unless otherwise specified:

- Concomitant medication
- Vital signs
- Biochemistry and haematology
- [redacted]
- [redacted]
- [redacted]
- AEs
- Ophthalmic examination
- CFP
- FAF

- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- Reading performance (MNRead)
- Visual function questionnaire (VFQ-25)
- FRI index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.14 *Visit 10, Week 72 (Local or Surgical Site)*

The following assessments will be performed for ALL subjects unless otherwise specified:

- Concomitant medication
- Vital signs
- Biochemistry and haematology
- AEs
- Ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- Reading performance (MNRead)
- Visual function questionnaire (VFQ-25)
- FRI index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)

- [redacted]

6.1.15 *Visit 11, Week 96/End of Study and Early Termination Visit (Local or Surgical Site)*

The following assessments will be performed in ALL subjects unless otherwise specified:

- Concomitant medication
- Vital signs
- Biochemistry and haematology
- [redacted]
- [redacted]
- [redacted]
- AEs
- Ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- Reading performance (MNRead)
- Visual function questionnaire (VFQ-25)
- FRI index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.16 *Unscheduled Visit*

If clinically indicated, subjects may need to return to the site for an unscheduled visit. The Investigator will perform assessments considered to be appropriate for the subject, considering

the reason behind the need to arrange an unscheduled visit. These results should be recorded in the subject's medical notes and eCRF.

7 STUDY ASSESSMENT

7.1 Demographic and Screening Assessments

Informed Consent Procedure

The informed consent process will be conducted prior to performing any study related procedures. Subjects entered into the study must have genotyping and serum CFI evaluation performed by a Sponsor-approved laboratory, either through participation in a previous Sponsor study, or during the HORIZON screening period. Informed consent will include permission for genotyping (genotyping and serum CFI evaluation are not required for subjects who have these data from another Gyroscope study) and a consent from each subject or legal representative to enrol into HORIZON and undergo ophthalmic and clinical assessments to determine eligibility for inclusion in the study. Data from subjects screened in another Gyroscope sponsored study at the same investigative site as HORIZON may be used to fulfil the screening and eligibility requirements for this study. This is only permissible if the screening data is collected within the screening period specified in the clinical protocol. Should subjects fail to meet the eligibility for HORIZON, they will be classed as Screen Failures for this study and may be considered for entry into another Gyroscope sponsored study.

[redacted]

It is the responsibility of the Investigator, or a suitably qualified person delegated by the Investigator to obtain written informed consent from each subject. The Investigator or designee will explain that the subject is under no obligation to enter the study and that they may withdraw at any time during the study, without having to give a reason.

A copy of the signed Informed Consent Forms (ICFs) will be given to the subject. The original signed form(s) will be retained at the study site.

Subject Eligibility

It is the responsibility of the Investigator, or a suitably qualified person delegated by the Investigator to confirm the eligibility of each subject for the study. Review and confirmation of eligibility is to be documented in the subjects' medical records.

Demographics

Subject demographics, including year of birth, race, ethnicity and sex at screening will be captured.

Medical/Surgical History

Prior medical history (including all ocular history) will be reviewed and recorded in the eCRF. This will comprise of (and be updated throughout the study):

- all current and prior ocular medical and surgical history
- all current and prior significant general medical and surgical history
- pertinent family (e.g. related parents and children) and social history

7.2 Concomitant Medication and Corticosteroid Compliance

7.2.1 *Concomitant Medication*

All concomitant medication will be reviewed and recorded, including:

- current medication use
- any drug allergy or contraindication to steroids

[redacted]

7.3 Ophthalmic Assessments

Details of the required assessments will be provided in the Central Imaging Manual.

Camera equipment used at investigative sites will be required to meet the specifications of the CRC as specified in the Central Imaging Manual.

7.3.1 *Ophthalmic Examination*

Ophthalmological examinations in both eyes will be performed as follows: anterior segment examination via slit lamp biomicroscopy, IOP via Goldmann applanation tonometry (GAT) or a Tono-Pen®, posterior segment and fundus examination via dilated indirect ophthalmoscopy. Ocular inflammation will be assessed.

Slit lamp will be conducted on both eyes. The eyelids, cornea, conjunctiva, anterior chamber, iris/pupil and lens should be evaluated. Findings will be graded as normal, abnormal non-clinically significant, or abnormal clinically significant. Cataract will be graded using the AREDS clinical lens grading system [Appendix 17.1]. IOP should be assessed using the same method (GAT or Tono-Pen®) throughout the study regardless of method chosen.

Dilated indirect ophthalmoscopy will assess the vitreous, macula, choroid, optic nerve, retina, and cup- to-disc ratio of both eyes. Findings will be graded as normal, abnormal non-clinically significant, or abnormal clinically significant.

7.3.2 *Pre-surgical Ocular Safety Check*

A pre-surgical ocular safety check should be performed to verify there are no new ocular adverse events that would halt surgery. Pre-surgical ocular safety checks should be performed as per local procedures and/or at the discretion of the Investigator assessing the subject.

7.3.3 *Colour Fundus Photography*

CFP of the fundus of both eyes will be performed by certified technicians following pupil dilation. All fundus photographs will be sent by the sites to the CRC for review (unless otherwise specified); the CRC will transfer the data to the data management group and/or ISC. For complete technical specifications for fundus photography, refer to the Central Imaging Manual (which will include procedures from the CRC regarding how measurements are to be taken).

7.3.4 *Fundus Autofluorescence*

To assess changes in the area of GA, FAF will be performed for both eyes.

All FAF images will be performed by certified technicians at the site after dilation of the subject's pupil and sent to a CRC for review; the CRC will transfer the data to the data

management group and/or ISC. For complete technical specifications for FAF, refer to the Central Imaging Manual (which will include procedures from the CRC regarding how measurements are to be taken).

7.3.5 *Optical Coherence Tomography (Macula [redacted])*

OCT is a method of using low-coherence interferometry to determine the echo time delay and magnitude of backscattered light reflected off an object of interest. This method can be used to scan through the layers of a structured tissue sample, such as the retina, with very high axial resolution (3 to 15 μm), providing images demonstrating three dimensional structure. Because of the unique optically clear pathway through the eye, OCT has been used most extensively for imaging disorders affecting the retina.

OCT will be performed for both eyes. OCT measurements will be taken by certified technicians at the site after dilation of the subject's pupil. All OCT scans will be submitted by the sites (unless otherwise specified) to a CRC where the scans will be evaluated. The CRC will transfer the data to the data management group and/or ISC. For complete technical specifications for OCT, refer to the Central Imaging Manual (which will include procedures from the CRC regarding how measurements are to be taken).

7.3.6 *Optical Coherence Tomography A*

OCT A allows for non-invasive evaluation of retinal and choroidal vascular abnormalities that is useful as a diagnostic tool for Investigators to identify CNV. Other imaging modalities as described in the Central Imaging Manual may be utilised to assess for CNV. OCT-A may be performed as clinically indicated during the course of the study, for example, if a subject converts to wet AMD.

7.3.7 *Fluorescein Angiography*

Fluorescein angiography is used to examine the circulation of the retina and choroid using a fluorescent dye and a specialised camera. Sodium fluorescein is added into the systemic circulation, the retina is illuminated with blue light at a wavelength of 490 nanometers, and an angiogram is obtained by photographing the fluorescent green light emitted by the dye.

Fluorescein angiography may be performed to assess CNV to confirm eligibility and as clinically indicated during the course of the study, for example, if a subject converts to wet AMD.

[redacted]

7.3.9 *Visual Acuity Check*

A visual acuity check using a Snellen chart (near card is permissible) must be performed pre-surgery on the study eye if >4 weeks have elapsed between BCVA with ETDRS and surgery. If the Snellen vision is >2 lines (BCVA equivalent to 10 letters) worsened compared to the previous BCVA with ETDRS, a BCVA with EDTRS must be repeated prior to surgery. If the BCVA with EDTRS results is ≤2 lines worsened compared to the previous BCVA with ETDRS, record the subjects vision in the eCRF and surgery can proceed. If the repeat BCVA with EDTRS check remains >2 lines (BCVA equivalent to 10 letters) worsened, surgery must be postponed pending discussion and approval by the Sponsor Medical Monitor.

7.3.10 *Best Corrected Visual Acuity*

To evaluate changes in visual acuity over the study period, BCVA will be assessed for both eyes using the ETDRS visual acuity chart.

The BCVA test should be performed prior to pupil dilation, and distance refraction should be carried out before BCVA is measured. Initially, letters are read at a distance of 4 metres from the chart. If <20 letters are read at 4 metres, testing at 1 metre should be performed. BCVA is to be reported as number of letters read correctly by the subject. At the Screening Visit, eyes with a BCVA of ≥24 ETDRS letters (6/95 or 20/320 Snellen acuity equivalent or better), using ETDRS charts will be eligible for the study.

If a subject cannot read any letters on the BCVA chart, the subject will be tested for finger counting, hand movements or light perception.

7.3.11 *Low Luminance Difference*

To evaluate the subject's low luminance deficit, LLD will be measured for both eyes. The test should be performed after BCVA testing, prior to pupil dilation, and distance refraction should be carried out before LLVA is measured. LLVA is measured by placing a 2.0-log-unit neutral density filter over the front of each eye and having the subject read the normally illuminated ETDRS chart. The LLD is calculated as the difference between BCVA and LLVA. Initially, letters are read at a distance of 4 metres from the chart in each eye. If <20 letters are read at 4 metres, testing at 1 metre should be performed.

7.3.12 *Reading Performance (MNRead)*

Monocular (study eye separate from contralateral eye) Reading Speed will be assessed by the MNRead acuity test [Appendix 17.2]. The reading test will be provided in the native language of the participating subject.

7.3.13 *Visual Function Questionnaire (VFQ-25)*

The VFQ-25 is a validated 25-item version of the 51-item visual function questionnaire developed at RAND under the sponsorship of the National Eye Institute [Appendix 17.3].

7.3.14 *Functional Reading Independence Index*

The FRI index is a patient-reported outcome measure developed specifically for use in GA patients [Appendix 17.5]. The FRI index evaluates the level of independence subjects have in performing everyday activities that require reading, such as writing a cheque or reading a prescription. Scores derived from the index range from 1 (unable to do) to 4 (total independence). The FRI index will be provided in the native language of the participating subject.

7.4 Safety

7.4.1 *Vital Signs*

Vital signs including heart rate, temperature, and blood pressure will be measured. Blood pressure (systolic and diastolic) to be measured in triplicate after five minutes rest in a sitting position. The same method should be used throughout the study. Heart rate will be assessed as a single measurement.

7.4.2 *Adverse Events*

Subjects will be questioned in a general way at each study visit to establish whether AEs have occurred since the previous visit (e.g. “How have you been feeling since your last visit?”). Additionally, the Investigator will evaluate other collected data (e.g. questionnaires) to ascertain whether an AE has occurred. All AEs will be captured from the time the subject provides written informed consent and monitored throughout the study. Additional imaging safety assessments may be collected at any visit, as needed, in order to follow-up on any AEs.

[redacted]

7.4.3 *Pregnancy Test*

Females of child-bearing potential are defined as those who have experienced menses in the past 12 months and do not meet the criteria for women not of child-bearing potential. Women not of child-bearing potential are females who are permanently sterile (e.g. bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) or post-menopausal. Post-menopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

Females of child-bearing potential will undergo urine pregnancy testing at Visit 1 (screening) and for those subjects allocated to GT005, an additional test prior to surgery on Day 1 (Visit 2).

7.4.4 *Laboratory Safety Tests*

Blood samples for serum chemistry and haematology will be taken for evaluation of laboratory safety parameters [Table 3]. The Investigator must review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF.

All clinically relevant laboratory test abnormalities occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator and the Sponsor Medical Monitor (or designated representative), or until the

abnormality is explained by an appropriate diagnosis. See Section 8 for abnormal laboratory tests that should be recorded as AEs in the eCRF.

The anticipated volume of blood samples collected during the study from each subject will not exceed 450 mL (over approximately 2 years).

Table 3: Laboratory Parameters

Panel	Parameter	Panel	Parameter
Biochemistry	Albumin	Haematology	Haemoglobin
	Alkaline phosphatase		Haematocrit
	Alanine aminotransferase		Mean corpuscular haemoglobin
	Aspartate aminotransferase		Mean corpuscular haemoglobin concentration
	Bicarbonate		Erythrocytes
	Bilirubin (Direct)		Leucocytes
	Bilirubin (Indirect)		Differential count:
	Bilirubin (Total)		Basophils
	Calcium		Eosinophils
	Chloride		Lymphocytes
	Creatine Kinase		Monocytes
	Creatinine		Neutrophils
	C-Reactive Protein		Large unstained cells
	Gamma glutamyl transferase		Platelets
	Globulin		
	Glucose (Random)		
	Lactate dehydrogenase		
	Lipase		
	Magnesium		
	Phosphate		
	Potassium		
	Protein Total		
	Sodium		
	Blood urea nitrogen		
	Estimated glomerular filtration rate (eGFR)[1]		

[1]eGFR will be calculated using the CKD-EPI (chronic kidney disease epidemiology collaboration) formula.

7.4.5 [redacted]

[redacted]

[redacted]

7.4.5.4 Genotyping

Subjects entered into the study must have genotyping performed by a Sponsor-approved laboratory, either through participation in a previous Gyroscope-sponsored study, or during the HORIZON screening period. [redacted]

8 ADVERSE EVENT REPORTING

All AEs will be captured from the date of written informed consent and monitored throughout the study. AEs will be elicited by direct non-leading questioning or by spontaneous reports.

8.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the IMP. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

Natural progression or deterioration of the (disease/symptoms) under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE.

8.2 Definition of Serious Adverse Event

A SAE is any AE that:

1) Results in death
2) Is life threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons
4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions
5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP
6) Is an important medical event that may not result in death, be life threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include a sight-threatening AE that requires surgical intervention to prevent permanent sight loss

In addition to the above criteria, any additional AE that an Investigator considers serious should be immediately reported to the Sponsor and included in the SAE database.

Hospitalisation is defined as any unplanned overnight admission into hospital. For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.

Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AEs (i.e. not associated with the development of a new AE or worsening of a pre-existing condition)

may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor.

Pre-planned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

8.3 Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. AESIs should also be assessed as to whether it fits the criteria of an SAE and reported appropriately. AESI should be reported as per reporting requirements (Section 8.5.1). [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

It is anticipated that there may be transient decreases to visual acuity related to the subretinal injection surgical procedure. A transient visual loss may be observed in the first days post-surgery due to bleb-related foveal detachment, if performed. Transient surgery-related events of decreases in visual acuity are defined as decreases occurring in close temporal association (within 24 hours) with the surgical administration of the study medication, and which are resolving at Week 1 (Visit 3) post-surgery.

Additionally, there is a known risk of cataract associated with any vitrectomy procedure. A published review from [Feng 2014] shows cataract to be common following pars plana vitrectomy with about 40% of patients requiring a cataract extraction over the following 2 years.

Transient, surgically-related decreases in visual acuity, as well as cataract will not be classified as AESI.

8.4 Classification of an Adverse Event

8.4.1 *Severity Assessment*

AEs will be classified as mild, moderate, or severe according to the following criteria:

Mild: Does not interfere with subject's usual function.

Moderate: Interferes to some extent with subject's usual function.

Severe: Interferes significantly with subject's usual function.

AE severity will be assessed at the site by the Investigator or a medically qualified designee.

8.4.2 *Causality Assessment*

The relationship of an AE to IMP or surgical procedures will be classified by the Investigator or medically qualified designee.

When assigning relatedness of the AE, consideration will be given to whether there is a plausible relationship to either the IMP or the surgical procedure.

The following are definitions of relatedness that will be used in this study:

- Related: reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship to the IMP or the surgical procedure. In the sense that it is plausible, conceivable or likely
- Not related: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship to the IMP or the surgical procedure with IMP administration
- Unknown: there is insufficient information to assess plausibility of causal relationship to the IMP or the surgical procedure

8.4.3 *Expectedness Assessment*

An expected adverse reaction is where the nature or severity of the AE is consistent with the applicable product information (as specified in the IB), otherwise it is considered unexpected.

8.4.4 *Action Taken Regarding the Investigational Medicinal Product*

The action taken regarding IMP must be described by selecting one of the following:

- No action taken (once GT005 is administered, this gene therapy cannot be removed)
- Drug withdrawn
- Dose reduced or partially administered
- Unknown or not applicable

8.4.5 *Outcome*

All AEs should have the outcome recorded as one of the following:

- Recovered or resolved
- Recovering or resolving
- Not recovered or not resolved
- Recovered with sequelae or resolved with sequelae
- Fatal
- Unknown

8.5 Reporting Requirements

8.5.1 *Serious Adverse Events and Adverse Event of Special Interest*

All SAEs/AESIs regardless of treatment group or suspected relationship to IMP or surgical procedure must be recorded and reported immediately (within 24 hours of the Investigator's knowledge of the event) to the pharmacovigilance contact specified below. If the immediate

report is submitted by telephone, this must be followed by detailed written reports using the relevant report form.
The SAE/AESI must be reported immediately (within 24 hours of awareness), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period.

The following information is the minimum that must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE/AESI:

- Study number
- Centre number
- Subject number
- AE
- Investigator name and contact details

The additional information included in the form must be provided to the Sponsor or representative as soon as it is available. The Investigator should always provide an assessment of causality for each event reported to the Sponsor. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

All SAEs/AESI must be reported in the eCRF. Alternatively, if the eCRF cannot be accessed, please contact [redacted] by telephone, fax or email:

[redacted] ***SAE hotline – Europe/Australia:***

Telephone: [redacted]

Fax: [redacted]

e-mail: [redacted]

[redacted] ***SAE hotline – United States:***

Telephone: [redacted]

Fax: [redacted]

e-mail: [redacted]

Where the Investigator requires advice regarding the handling of SAEs/AESIs, the contact in case of emergency is:

[redacted] ***(Europe/Australia only)*** [redacted] ***(United States only)***

8.6 Follow-up of Adverse Events

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the eCRF.

Any AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, and where possible, sufficient information reviewed to assess causality of the AE (i.e. IMP, surgical procedure, or other illness). The Investigator is required to assess causality and record that assessment on the eCRF.

AEs will be followed until the event has resolved, subsided or stabilised. This includes those subjects allocated to GT005 who are enrolled in the long-term follow-up study (ORACLE).

Subjects who are withdrawn from the study as a result of an IMP-related AE will be followed up until the event has resolved without sequalae, subsided, stabilised, or the subject withdraws consent or is lost to follow-up.

All SAEs, regardless of attribution to IMP or the surgical procedure, should be followed-up until the event has resolved without sequalae, subsided, stabilised, or the subject withdraws consent or is lost to follow-up. The Sponsor (or designee) will follow-up SAE reports to completion. Investigators are expected to timely provide the requested additional information for a complete assessment and documentation of the SAE reports.

8.7 Pregnancy

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] Clinical Safety within 24 hours of knowledge of the event. [redacted] Clinical Safety will then provide the Investigator/site the exposure in utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted] Clinical Safety. Pregnancies will be reported from the time of treatment administration until the end of the study.

The Investigator must instruct all female subjects of child-bearing potential to inform them immediately should they become pregnant during the study. The Investigator should counsel the subject, discuss the risks of continuing with the pregnancy, and the possible effects on the foetus. The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the follow-up EIU form should be completed and faxed/emailed to [redacted] Clinical Safety. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

If the female partner of a male subject becomes pregnant after the subject has received IMP or within the safety follow-up period, the Investigator should notify [redacted] Clinical Safety as described above. After the partner has provided written consent, she should be counselled and follow the same procedures as a female participant in the study who becomes pregnant. Monitoring of the partner should continue until conclusion of the pregnancy as outlined above.

8.8 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

If the subjects withdraws from the study due to an AE,SAE, or AESI, every effort should be made to follow-up on any ongoing AEs. Any subject treated with GT005 should receive appropriate medical follow-up.

8.9 Reporting to Competent Authorities/Ethics Committees/Other Investigators

The Sponsor will ensure that processes are in place for submission of reports of suspected unexpected serious adverse reactions (SUSARs) occurring during the study to the Competent Authorities, IEC or IRB and other investigators. Reporting will be done in accordance with the applicable regulatory requirements.

For study centres in the United States, Investigational New Drug application safety reports will be submitted directly to the investigators. It is the Investigators' responsibility to notify their IEC or IRB in a timely manner.

9 STATISTICS METHODS

9.1 Sample Size Determination

Untreated control mean GA change at 72 weeks was assumed to be 3.0 mm^2 with standard deviation (SD)=1.5 mm^2. The following hypotheses are considered:

$$H0_M: \mu_M - \mu_C = 0, HA_M: \mu_M - \mu_C < 0$$

$$H0_H: \mu_H - \mu_C = 0, HA_H: \mu_H - \mu_C < 0$$

Where μ_M, μ_H and μ_C represent the unknown true mean GA change on FAF at 72 weeks in the GT005 medium dose [redacted], GT005 high dose [redacted] and pooled untreated control, respectively.

The total sample size planned is approximately 250, accounting for an estimated 15% of subjects that are expected to discontinue treatment and not provide the target 72-week observation; hence power calculations are based on n=70 per treatment group (GT005 medium dose [redacted], GT005 high dose [redacted], pooled untreated control). [redacted]

9.2 Analysis Populations Definitions

The Full Analysis Set (FAS) will include all subjects who are randomised to GT005 or untreated control. The Safety Analysis Set (SAF) will include all subjects who are randomised to GT005 or untreated control, and have at least one post-baseline observation.

9.3 Significance Testing and Estimations

Type I error (alpha) is set at 0.05 one-sided and estimates of outcome parameters will be accompanied by 90% confidence intervals. [redacted]

9.4 Statistical/Analytical Methods

9.4.1 *Demographics and Baseline Characteristics*

Demographic and baseline characteristics including age, race, (self-reported and genetically defined) ethnicity, sex, AMD genetic subgroup, and baseline GA lesion size, will be summarised with descriptive statistics or counts and percentages of subjects as appropriate by treatment group and in total for each defined analysis population.

9.4.2 *Efficacy Assessments*

Efficacy assessments include ophthalmic imaging and examinations.

The primary estimand will focus on the effect attributable to different doses of GT005 on GA change on FAF at Week 72 by taking into account any potential unfavourable effects of GT005. The primary estimand is defined by the following elements:

- Population: Subjects with GA secondary to AMD
- Variable: Change from baseline in GA lesion size on FAF at Week 72
- Treatment: The randomised treatment (different doses) of the investigational therapy GT005, assuming no further benefit for subjects who withdraw from the study due to AEs or who receive alternative therapies for GA.
- Intercurrent events: defined in Table 4 .

Table 4: Intercurrent Events and Corresponding Primary Data Handling Strategies.

Intercurrent event	Data handling strategy
Subject receives alternative GA medications or therapies in the study eye	GA lesion size data collected in the study eye after the subject initiates alternative GA medications or therapies will be censored and imputed assuming no further benefit.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] Further details on data imputation approaches will be presented in the SAP prior to DBL.

The primary endpoint, change from baseline to Week 72 in GA area, will be estimated among treatment groups via least squares means from a mixed model repeated measures analysis (MMRM) analysis. Details of the MMRM specifications will be described in the SAP. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Other continuous efficacy endpoints will be analysed similarly using MMRM. All statistical tests will be at the nominal 0.05 one-sided level.

[redacted]

Categorical and binary endpoints will be summarised by counts and percentages by dose. No statistical inferential testing is planned for categorical and binary endpoints.

9.4.3 *Safety Assessments*

Safety evaluations include AEs, ophthalmic imaging and examinations, vital signs, laboratory safety (biochemistry and haematology).[redacted]

AEs will be summarised in two parts: systemic events and ocular events. For systemic events, data will be displayed according to treatment allocation (GT005 and untreated control). Ocular events will be displayed according to treatment allocation (including GT005 dose and untreated control) and study eye (study eye and contralateral eye).

All AEs (overall, by seriousness, by severity, by relationship), including AESI of special interest, recorded throughout the investigation will be reported following classification according to the Medical Dictionary for Regulatory Activities (MedDRA).

Systemic safety evaluations including vital signs, laboratory safety [redacted] will be summarised over time by dose (where applicable) and overall.

Ocular safety evaluations including ophthalmic examination variables (cataract grading, IOP, etc.) and BCVA scores, will be summarised in the same manner as ocular efficacy variables, dependant on data type.

[redacted]

9.5 72-Week Readouts

The analysis based on the Week 72 data will be the primary efficacy analysis for this study. The database including all Week 72 data will be locked once all enrolled patients from both Stage 1 and Stage 2 have completed the Week 72 visit or terminated the study prior to Week 72. Subjects will remain in the study and will continue their scheduled visits and assessments through the planned study duration of 96 weeks, to allow for further evaluation of efficacy and safety.

9.6 Data Monitoring Committee

A DMC will perform safety reviews of unmasked data as well as an evaluation of clinical outcomes, and may recommend stopping a dose, dose adjustment, adjusting the design of the study or stopping the clinical study altogether. The DMC will be provided unmasked data by an ISC as per DMC Charter to ensure safety of the subjects. Only the DMC and ISC will be unmasked to study data during the conduct of the study.

The DMC is an independent committee that will consist of three or more individuals who cumulatively have the clinical, surgical, medical, and statistical expertise to monitor the safety of subjects in the clinical study.

No DMC member will be an Investigator in the study. Full details regarding the DMC mission and content, and DMC reviews are detailed in the DMC Charter and in the SAP.

9.7 Handling Missing Data

Missing or censored data will be handled in accordance with the data handling strategy for intercurrent events as described in Table 4. The details of the statistical approaches for missing and/or censored data imputation will be described in the SAP, and may include additional missing data handling rules.

10 STUDY MANAGEMENT

10.1 Monitoring Procedures

The Investigator is responsible for the validity of all data collected at the site. The Sponsor is responsible for monitoring this data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, Good Clinical Practice (GCP) and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The Investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

The site must complete the eCRFs according to the eCRF Completion Guidelines, on an ongoing basis to allow regular review by the study monitor, both remotely via the internet and during site visits. The study monitor will use functions of the eCRF to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the Sponsor (e.g. laboratory print-outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

10.2 Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The Investigator must record all data relating to protocol procedures, IMP administration, laboratory data, safety data, and efficacy ratings on the eCRFs provided for the study. The Investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF. Subject questionnaires will be printed or electronic.

The Investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the Investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change will be required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

10.3 Source Data Verification

The study monitor will perform source document verification (SDV) according to the study monitoring plan. The study monitor will indicate verification by electronically applying SDV flags to the eCRF and will ensure that all required electronic signatures are being implemented accordingly.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Inspections and Auditing Procedures

Authorised personnel from external Competent Authorities and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory, and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and Inspectors must have direct access to study documents and site facilities, and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor's representative as soon as possible, to assist with preparations for the inspection.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Quality

The handling of data, including data quality assurance, will comply with regulatory guidelines (e.g. ICH and GCP) and the Sponsor's (or designee) standard operating procedures and working instructions. Data management and control processes specific to this study will be described in a Data Management Plan. All steps and actions taken regarding data management and quality assurance will be documented in a Data Handling Report. Data management will implement edit checks on the eCRF to enforce data entry guidelines, data consistency, and compliance to the protocol and regulatory requirements. The site Investigator or designee will be responsible for entering study data on the eCRFs. Data management will track eCRFs and review them for completeness, the presence of mandatory values, consistency, and dated electronic signatures. In addition to checking for SDV flags, data management will electronically attach data clarification queries directly onto the eCRFs during the review process to ensure data quality. Once study centre personnel have provided acceptable responses to the queries and implemented the changes on the eCRFs, data management will close the queries with the appropriate resolution status.

At the end of the study, the database will be locked and the data will be released for reporting and statistical analysis.

12.2 Data Management

An eCRF will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only Sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a Contract Research Organisation (CRO), directed by the Sponsor. All data management procedures will be completed in accordance with the Sponsor and the contracted CRO standard operating procedures.

The Sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The Investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the eCRF. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The Sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the Sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history, and concomitant medication terms will be performed by the contracted CRO, and reviewed and approved by the Sponsor. Concomitant medications will be coded using World Health Organisation DRUG and AEs/medical history terms will be coded using MedDRA.

12.3 Sponsor Discontinuation Criteria

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation with all parties.

12.4 Subject and Data Confidentiality

All information obtained during the conduct of the study with respect to the subject will be regarded as confidential. Personally Identifiable Information/Personal Health Information from or about a subject will not be collected by the Sponsor. The collection and processing of personal data will be limited to those data that are necessary to investigate the efficacy, safety, tolerability, quality, and utility of the IMP used in this study, and these data will be subject to applicable data privacy protection laws and regulations.

12.5 Sample Preparation, Handling and Storage

All biological samples will be collected by an appropriately trained healthcare professional and handled as per the relevant laboratory procedures manual. Sample collection tubes will be supplied by the central laboratory and will be labelled with waterproof labels containing appropriate study identifiers (e.g. protocol number, subject number, date of sample collection and visit number). Once collected, samples will be shipped to the central laboratory for analysis. Biological samples will be retained until all required analysis have been completed or a period of up to 5 years after completion of the study, whichever is sooner.

12.6 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product or for as long as necessary to comply with applicable legislation. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

The Sponsor is responsible to ensure that the collection and evaluation of data by vendors adheres to protocol specifications. Electronic data from the Sponsors contracted vendors will be archived by the Sponsor.

13 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

13.1 Institutional Review Board/Independent Ethics Committee Ethical Conduct of the Study

This study must be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki, ICH GCP Guidelines, and the FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerised Systems Used in Clinical Trials.

In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the Investigator or Institution should have written and dated approval/favourable opinion from the IEC or IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects, and a statement from the IEC or IRB that they comply with GCP requirements. The IEC or IRB approval must identify the protocol version as well as the documents reviewed.

After IEC or IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC or IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by the local or site IEC or the IRB.

13.2 Subject Information and Consent

Following consent subjects will undergo screening assessments for HORIZON to determine eligibility for inclusion in the study.

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject or impartial witness. Sufficient time will be allowed to discuss any questions raised by the subject.

[redacted]

The Sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the Sponsor and the IEC or IRB, and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent form.

The informed consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC or IRB. It is the Investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The Investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

Written and/or oral information about the study in a language understandable by the subject will be given to all subjects.

13.3 Reporting of Significant Safety Issues and Serious Breaches of the Protocol or ICH GCP

A significant safety issue or a serious breach is defined as a breach likely to affect, to a significant degree, the safety and rights of a subject or the reliability, and robustness of the data generated in this clinical study. In the event of a significant safety issue or a serious breach, the Sponsor shall inform the Competent Authority and IEC or IRB within 7 days of becoming aware of the breach.

14 ADMINISTRATION PROCEDURES

14.1 Regulatory Approval

The study will be authorised by the Competent Authority.

Enrolment of subjects will not start until approval has been received from both the IEC or IRB and Competent Authorities.

The study will be conducted in accordance with the Declaration of Helsinki, GCP and all other national requirements.

14.2 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including Medical Writers or Statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this study may be published in line with International Committee of Medical Journal Editor guidelines and internal procedures or communicated at scientific meetings. A plan for scientific publication and presentation of the results will be developed and implemented by the Sponsor.

The procedures for publications and data presentations are set out in the clinical study agreement entered into with the Sponsor (or designee) in connection with this study.

14.3 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has provided written informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

14.4 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. [redacted]

Financial Disclosure Statements will need to be completed as per local regulatory requirements.

14.5 Insurance, Indemnity and Compensation

[redacted]

For covered clinical studies (see 21CFR54), the Investigator will provide the Sponsor with financial information as per local regulatory requirements. Each Investigator will notify the Sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

15 PROTOCOL AMENDMENTS

15.1 Protocol Amendments and Protocol Deviations

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC or IRB and Competent Authority, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The Investigator and the Sponsor will sign the protocol amendment.

In the event that an amendment to this protocol is required, it will be classified into one of the following three categories:

- **Administrational changes** are those that are not considered 'substantial' (e.g. administrative changes) and as such are not required to be notified to the IECs/IRBs or Competent Authorities but are contained in the protocol under a subsequent notification of a substantial amendment
- **Substantial amendments** are those considered 'substantial' to the conduct of the clinical study where they are likely to have a significant impact on:
  - the safety or physical or mental integrity of the subjects
  - the scientific value of the study
  - the conduct or management of the study, or the quality or safety of the IMP used in the study

Substantial amendments must be notified to the IEC or IRBs and Competent Authorities. Prior to implementation, documented approval must be received from the IEC or IRB.

- **Urgent amendments** are those that require urgent safety measures to protect the study subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IEC/IRB and Competent Authority notification, forthwith

15.2 Protocol Deviations and Exceptions

A protocol deviation is non-adherence to protocol specific study procedures or schedules or the requirements of ICH-GCP that have been identified retrospectively. Protocol deviations are not acceptable from a regulatory perspective and any deviation not supported by an amendment will be considered a potential breach of GCP. Deviations from the protocol should only occur when necessary to eliminate immediate hazards to the subjects.

Protocol deviations will be identified and recorded by investigative site personnel on the eCRF and by the study monitor in the Monitoring Visit Reports and/or electronic data capture. Protocol deviations must be reported to Competent Authorities and IRB or IEC as per local or national guidelines.

As a matter of policy, the Sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If such an action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the Sponsor and the responsible IEC or IRB, in accordance with the standard operating procedure, is required before the subject will be allowed to enter the study. If investigative site personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study, they must immediately inform the Sponsor.

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17 APPENDICES

17.1 Age-Related Eye Disease Study Clinical Lens Grading System

Overview

The age-related eye disease study (AREDS) developed the Clinical Lens Grading System for grading the presence and severity of nuclear, cortical and posterior subcapsular (PSC) lens opacities (the three main types of age-related cataract) in a clinical setting. The system was designed to require minimal examiner training for persons already proficient in the use of the slit lamp.

General Instructions

Dilation – Pupils should be dilated to at least 5mm.

Grading of opacities – the lenses are examined at the slit lamp with 10× magnification for the presence and severity of the types of lens opacity: Nuclear, cortical and posterior subcapsular. For each type of opacity the examined lens will be compared to a series of three reference standard photographs combined onto one print. The severity of opacity witnessed of the lens being assessed will be determined to equal the opacity on one of the three reference photographs or have an opacity which falls in between two of the reference standard photographs.

Grading of Nuclear sclerosis

Nuclear Landmarks - In the normal or non-sclerotic lens, the "nucleus" consists of a central dark interval (sulcus), adjacent bean-shaped brighter areas (lentils—one anterior and one posterior to the sulcus), and brighter curved bands (lamellae, or nuclear surface bands) anterior and posterior to the lentils and separated from them by narrow dark bands.-Although nuclear sclerosis standard 1 shows signs of moderate opalescence, many of these features are visible.

For grading the severity of nuclear sclerosis two factors are considered:

I. The optical density of the nuclear landmarks, especially the sulcus

II. The definition of these structures (contrast between light and dark bands)

Optical density is given greater weight. In the early stages of nuclear sclerosis, increased optical density is noticeable only in the normally dark bands, particularly the sulcus, but in advanced stages the density of all bands becomes greater. With increasing nuclear sclerosis, the definition of nuclear landmarks decreases, and finally disappears. For grading nuclear status the primary consideration is the degree of reflectance (sometimes termed "opalescence") of the sulcus, with secondary consideration given to the definition of the nuclear features, i.e. contrast of the dark and bright bands.

Nuclear standard photographs - Three standard photographs with increasing amounts of nuclear opalescence are used for grading.

In nuclear standard 1 the density of the sulcus has increased so that only a suggestion of the sulcus can be detected. Towards the upper and lower ends of the sulcus, segments of what appears to be the equator of the fetal nucleus (or a zone just beneath its surface) are visible as steeply curved white lines. Only a small part of the anterior lentil is visible. The posterior nuclear surface band cannot be seen at all and the anterior one is very faint.

In nuclear standard 2, the sulcus has become so dense that only a faint shadow marks its location at the center of the lens, and the entire nucleus has become dense enough that lentils and lamellae are not distinguishable.

Nuclear standard 3 shows a further increase in nuclear density, to the point that neither the sulcus nor other features are distinguishable.

Slit lamp settings - Grading of nuclear opalescence is done with the illuminating beam of the slit lamp angled at 45° to the viewing axis, the slit beam width set at 0.3mm and the slit beam height set at 9mm.

Codes for nuclear grading –

I. None (grade 0)

II. Mild (grade 1)

III. Moderate (grade 2)

IV. Severe (grade 3)

Grading of Cortical Opacities

Grading of cortical opacities is done at the slit lamp using a red reflex image. The slit beam height and width are set by the assessor according to their usual practice as long as retroillumination is obtained. The position may be changed as needed so that all areas of the lens can be viewed against the red reflex. With retroillumination cortical opacities appear darker than the adjacent red reflex.

An area is considered involved by opacity if it is definitely more opaque than adjacent uninvolved areas. Opacities not seen against the red reflex are not counted. For comparison with the standard photographs, all areas of opacity are mentally rearranged into a contiguous mass and the total area of involvement is compared with the standard photographs. Vacuoles (small round cyst-like features) are not considered to be part of cortical opacity unless they are organised, e.g., part of a linear formation. When determining the extent of involvement, sizable clear areas bounded by opacity are subtracted from the total. Areas occupied by posterior cortical opacities that are not overlapped by anterior cortical opacities are added to obtain the total area of involvement. The density of opacity is not taken into account. Cortical and PSC opacities are differentiated from each other mainly by location, and secondarily by configuration.

Cortical standard photographs - Cortical opacities typically are wedge-shaped and radially oriented, extending from the periphery toward the center. Their appearance varies from dense opacity to diffuse collections of dots separated by clear areas.

Three standards with increasing amounts of cortical opacity are used for grading cortical opacities. In each standard the dashed white line defines the margins of the opacities.

In cortical opacity standard 1, three small spokes project in from the periphery between 5 and 7 o'clock, with a clear space between the spokes at 5:00 and 5:45.

In standard 2, a pie-shaped wedge extends from 3 to 6 o'clock, with a separate small spoke at 2:30.

standard 3 shows a semi-circle of cortical opacity extending from 3:30 to 9:30, with a dense spoke projecting from it centrally, and a group of vacuoles near the 3:30 margin (included as opacity because they are organised).

Codes for cortical grading - Grading of cortical opacities is done by comparing the proportion of pupillary involvement with cortical opacities in the lens to be graded and the proportion of involvement in the standard photographs. Only opacities seen against the red reflex image are counted.

Cortical percent involvement of the entire visible lens:

I. 0-10% (grade 0)

II. 10-25% (grade 1)

III. 25-50% (grade 2)

IV. >50% (grade 3)

Grading of Posterior Subcapsular Opacities:

Grading rules are similar to those for cortical opacities except that the red reflex image is focused at the plane of the posterior capsule. In this position the pupillary margin should be blurred. PSC opacities are considered to be present only when an area is definitely more opaque than adjacent areas as seen against the red reflex. For comparison with the standard photographs, all areas of PSC opacity are mentally rearranged into a contiguous mass and the total area of involvement is compared with the standard photographs. Mittendorf dots are disregarded. The density of PSC opacities is not taken into account.

PSC opacities are seen just beneath the posterior lens capsule. Frequently they are centred near the posterior pole of the lens. Although they usually appear as a lacy configuration which may contain vacuoles (any such are considered part of PSC), they may range from a darkly opaque network to a barely discernible diffuse haze. Because PSC opacities are fairly compact with few clear areas, small spaces within PSC are not subtracted from the estimate of extent.

Three standard photographs with increasing amounts of PSC opacity are used for grading PSC opacities. In each standard the dashed white line defines the margins of the opacities.

In PSC standard photograph 1, a roundish opacity is located just left of centre in the photograph.

In PSC standard 2 a larger opacity, also left of centre, includes vacuoles around nearly half of its perimeter. Within its margins of the density of the involved area is uneven, but the entire region is considered opacified.

PSC standard 3 shows a roundish opacity that is even larger and involves the centre of the lens. (An array of cortical spokes, located peripherally between 6:30 and 10:00 and rather unfocused, is not considered part of PSC.)

PSC grading is done by comparing the size of the PSC opacity in the lens to be graded with the size of the PSC opacity in the standard photographs. Only opacities seen against the red reflex image are counted.

PSC percent pupillary involvement of the 5mm diameter central circle of the lens:

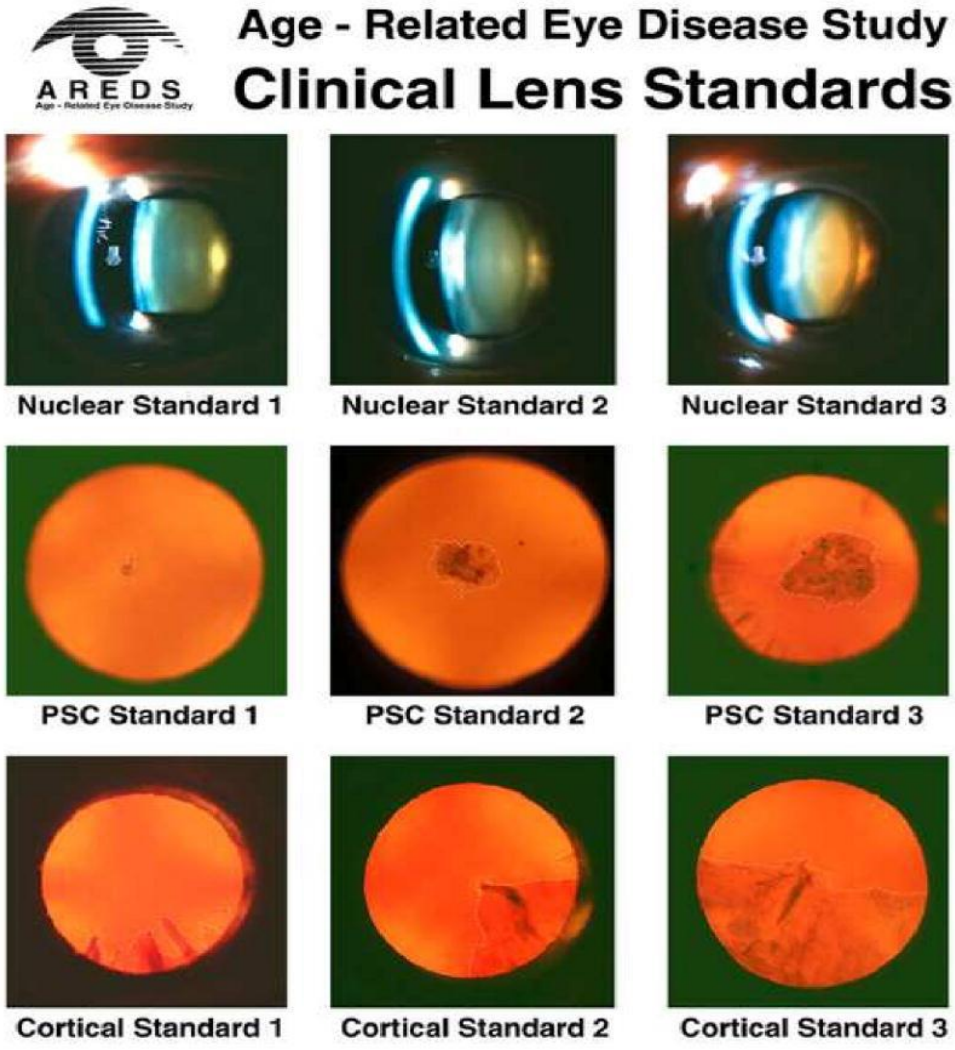
I. 0-2% (grade 0)

II. 2-20% (grade 1)

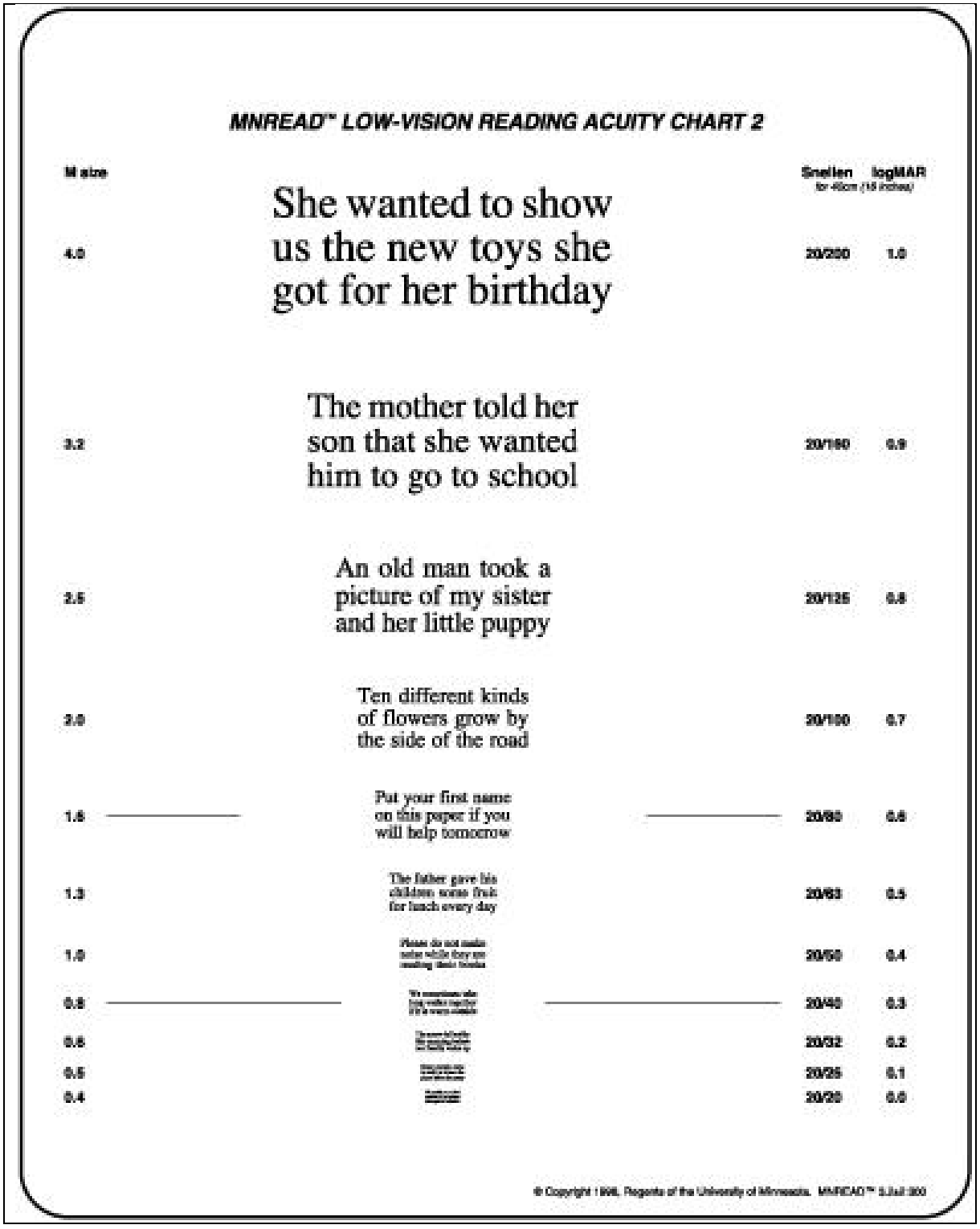
III. 20-50% (grade 2)

IV. >50% grade 3)

Reference Photographs taken from: [Chew 2010]



17.2 Reading performance (MNRead)



MNREAD™ LOW-VISION READING ACUITY CHART 2

M size		Snellen (for 40cm / 16 inches)	logMAR
4.0	She wanted to show us the new toys she got for her birthday	20/200	1.0
3.2	The mother told her son that she wanted him to go to school	20/160	0.9
2.5	An old man took a picture of my sister and her little puppy	20/125	0.8
2.0	Ten different kinds of flowers grow by the side of the road	20/100	0.7
1.6	Put your first name on this paper if you will help tomorrow	20/80	0.6
1.3	The father gave his children some fruit for lunch every day	20/63	0.5
1.0	Please do not make noise while they are reading their books	20/50	0.4
0.8	We sometimes also buy other fruit for it is very useful	20/40	0.3
0.6	[illegible]	20/32	0.2
0.5	[illegible]	20/25	0.1
0.4	[illegible]	20/20	0.0

17.3 Visual Function Questionnaire (VFQ-25)

Visual Function Questionnaire (VFQ-25) developed at RAND under the sponsorship of the National Eye Institute.

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

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version 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. **In general, would you say your overall health is*:**

(Circle One)

READ CATEGORIES:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. **At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?**

(Circle One)

READ CATEGORIES:

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?
(Circle One)

READ CATEGORIES:

None of the time	1
A little of the time	2
Some of the time	3
Most of the time	4
All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:
(Circle One)

READ CATEGORIES:

None	1
Mild	2
Moderate	3
Severe, or	4
Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ..... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty 4

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16. How much difficulty do you have driving at night? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

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PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

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For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me...	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A7. **Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

A8. **Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

SUBSCALE: SOCIAL FUNCTION

A9. **Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?**
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

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SUBSCALE: DRIVING

A10. **[This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]**

SUBSCALE: ROLE LIMITATIONS

A11. **The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.**
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?.....	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?.	1	2	3	4	5

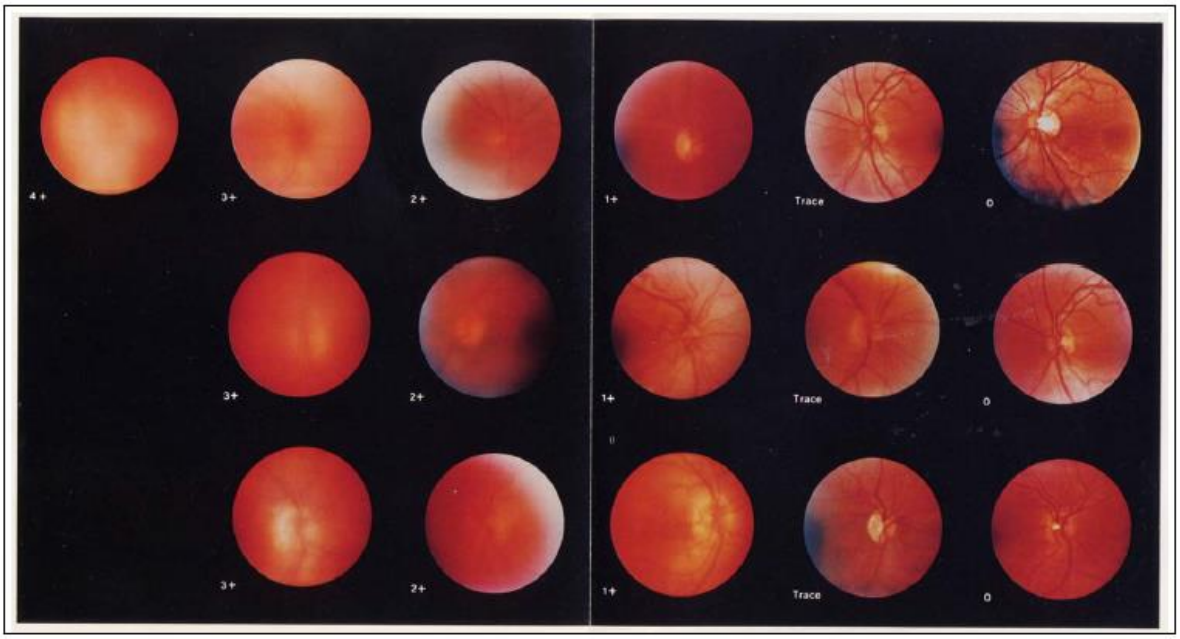
SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.....	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.	1	2	3	4	5

17.4 Vitreous Haze Grading Scale



NUSSENBLATT CHART

Nussenblatt RB, Palestine AG, Chan CC, et al., Standardization of vitreal inflammatory activity in intermediate and posterior uveitis, Ophthalmology, 1985;92:467–71.