EXPLORE: A PHASE 2, OUTCOMES ASSESSOR-MASKED, MULTICENTRE, RANDOMISED 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 AGE-RELATED MACULAR DEGENERATION

STUDY PROTOCOL

STUDY NUMBER:	GT005-02 / NCT04437368
VERSION:	6.0
DATE:	06 DEC 2022
SUPERSEDED VERSION/DATE:	5.0 (03 June 2021)
PRODUCT NAME/CODE:	GT005 A RECOMBINANT, NON-REPLICATING ADENO-ASSOCIATED VIRAL VECTOR SEROTYPE 2 (AAV2) EXPRESSING HUMAN COMPLEMENT FACTOR I
EudraCT NUMBER:	2019-003421-22
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
[redacted]	[redacted]
[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
AREDS	Age-related eye disease study
ATA	Anti-transgene antibodies
BCVA	Best corrected visual acuity
BSS	Balanced salt solution
C3	Complement component 3
CFI / CFI	Complement factor I (*gene* / protein)
CFP	Colour fundus photography
CFR	Code of Federal Regulations
CNV	Choroidal neovascularisation
CRC	Central Reading Centre
CRO	Clinical Research Organisation
CSR	Clinical study report
DBL	Database lock
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee
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 consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive response technology
ISC	Independent Statistics Centre
LLD	Low luminance difference
LLVA	Low luminance visual acuity

Abbreviation	Definition
MedDRA	Medical dictionary for regulatory activities
MAIA	Macular Integrity Assessment
MHRA	Medicines and Healthcare Products Regulatory Agency
MMRM	Mixed model repeated measures
[redacted]	[redacted]
NA	Not applicable
NHP	Non-human primate
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography-angiography
QID	Four times daily
PRL	Preferred retinal locus
PSA	Prostate-specific antigen
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SDV	Source data verification
SUSAR	Suspected unexpected serious adverse reactions
Tel	Telephone
V	Visit
[redacted]	[redacted]
Vg	Vector genomes

PROTOCOL SIGNATURES

Investigator Agreement and Signature:

I, the undersigned, have read and understood the GT005-02 EXPLORE 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:

NAME: [redacted] MA MB BChir MSc SIGNATURE: DocuSigned by: [redacted]

TITLE: [redacted] Clinical Development DATE: [redacted]

AMENDMENT HISTORY

Protocol Version	Change	Justification
V1.0, 13 Sept 2019 (Initial)	NA	NA
V2.0, 31 Oct 2019	• Primary Endpoint	• Correction of administrative error to align primary endpoint with wording in the protocol body, and clarify GA measurement is from baseline to Week 48
	• Number of Subjects	• Number of subjects increased from 48 to 54 to include an assumed 10% withdrawal rate
	• Masking	• Clarified that the primary endpoint is masked to the assessor, and that the assessor will receive the same images for all subjects in order to maintain masking
	• Screen Failures and Replacements	• Clarified that subjects who are withdrawn from the study after randomisation will not be replaced
	• Contraception	• Definition of true abstinence added, in response to MHRA grounds for non-acceptance
	• Long-term Follow Up	• Clarified that the long-term follow-up will be performed in a separate study under a separate consent
	• Formulation, Appearance, Packaging and Labelling	• Changes made to reflect compliance of labelling requirements with Competent Authority regulations in EU, USA and RoW
	• Protocol Deviations and Exceptions	• Clarification of handling of protocol deviations, in response to MHRA grounds for non-acceptance
V3.0, 13 May 2020	• Dose rationale updated	• Incorporated data from completed dose escalation from FOCUS (Phase 1/2 study)
	• Number of subjects enrolled	• Number of subjects increased to 75 to adequately power for a stastitically significant effect assuming the true underlying change in GA area is inhibited by a 40% treatment effect
	• Schedule of Assessments	• Screening period extended, incorparated a requirement for a pre-operative vision check if previous vision >4 weeks prior for patient safety and incorporated requirement of PRL identification pre-operatively. Clarified reporting of related SAEs from time of consent and all AEs from time of randomisation
	• Inclusion/Exclusion Criterion	[redacted]
	• Clarification regarding performing and obtaining genotyping results prior to commencement of screening assessments.	• Given the low prevalance of CFI mutations and desire to minimise patient study activities, genotyping results will be received to confirm eligibility prior to other screening activities commencing
	[redacted]	[redacted]

Protocol Version	Change	Justification
	[redacted]	[redacted]
	• Additional Week 8 Visit added.	• To support additional safety monitoring, [redacted]
	[redacted]	[redacted]
	• Removed requirement to remain in medical facitility overnight following surgery.	• Emerging safety profile from the completed dose escalation in the Phase 1/2 FOCUS does not support need for overnight stay in a medical facility
	[redacted]	[redacted]
	• Potential risk section updated.	[redacted]
	[redacted]	[redacted]
	• Updated guidance on GT005 destruction.	• Provide more detailed instruction and clarity
	• Throughout the document	• Inconsistences removed and language clarified. As these are minor revisions, they have not been summarised
V4.0, 13 NOV 2020	• Extension of the duration of subject participation from 48 to 96 weeks	• Subject participation duration has been extended to 96 weeks to enable the generation of long term treatment effects and durability of effect
	• Inclusion/Exclusion Criterion	• Inclusion criterion 3 has been updated to ensure subjects have dry AMD and/or GA, secondary to AMD in both eyes • Exclusion criterion 4 added to provide clarification on required duration of prior intraocular surgery before screening • Inclusion criterion 6 broadened to BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent), to evaluate the treatment effect of subjects with worse-seeing vision • Inclusion criteria 7 revised to include an evidence-based approach to enrolment of subjects into the study • Inclusion criterion 8 no longer required as genotyping requirements have been included in criterion 7 • Exclusion criterion 12 updated to broaden the malignancies/cancer types excluded from the study
	• Inclusion of additional secondary efficacy endpoint • Corrected the imaging modality for retinal anatomical measures	• Inclusion of new secondary efficacy endpoint measurement during the newly added second year of subject participation • Updated terminology to multimodal imaging as CFP is not the only imaging modality used to measure retinal anatomical measurements
	[redacted]	[redacted]

Protocol Version	Change	Justification
	[redacted]	[redacted]
	[redacted]	[redacted]
	• Inclusion of FA assessment	• FA included as an assessment to verify subjects do not have CNV at baseline or conversion to CNV during the study. • Addition that all unscheduled FA images to be sent to CRC
	• Additional OCT-A	• OCT-A imaging added, if required, to identify potential CNV conversion during the study
	• Clarification of OCT modalities	• The differing OCT modalities have been clarified: OCT-A (for monitoring of CNV conversion), OCT macula [redacted] to provide clarity to investigational sites and to add further timepoints if required by the Investigator to detect any safety changes on the retina, [redacted] any other safety-related changes
	• Randomisation to either eye (if both eligible) removed • Genotyping ICF	• The eye with worse visual acuity will be selected, if both eyes are eligible to help safeguard vision in the better seeing eye • Separate Genotyping ICF created to fulfil genotyping requirements prior to performing full screening assessments for eligible subjects
	• Pre-surgical ophthalmic checks	• Clarification regarding the extent of pre-surgical ophthalmic examination
	• AE Reporting language • Removal of reference to PRL identification prior to surgery	• Safety reporting requirements updated to collect all AEs from date of signed consent • The retinotomy site has been relocated to outside the vascular arcades. The revised retinotomy location will not encroach on the Preferred Retinal Locus (PRL) and therefore the requirement to identify the PRL has been removed
	[redacted]	[redacted]
	• Throughout the protocol	• Alignment of use of consistent dosing nomenclature from “Dose 1” and “Dose 2” to “low dose [redacted]” and “high dose [redacted] vg]” respectively • Administrative inconsistences removed and language clarified. As these are minor revisions, they have not been summarised
V5.0, 03 JUN 2021	• Inclusion/Exclusion Criterion	• Inclusion criterion #6 and exclusion criterion #1 altered to allow inclusion of patients with CNV/wet AMD in fellow eye
	• Stratification of subjects with fellow eye CNV	• Subjects with fellow eye CNV will be stratified across all three treatment groups: high-dose, low-dose and control

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 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 CFI threshold • Correction of erroneous footnote number at Early Termination Visit [redacted] • Sponsor address updated
V6.0, 06 DEC 2022	• Study design has been amended so that Part 1 provides an evaluation of CFI rare variant GA subjects with the low and high dose of GT005 compared with untreated control, and Part 2 evaluates the broad genetic GA population with the low dose of GT005 compared with untreated control. The overall study sample size has been increased to approximately 202.	• In its current form, the study is unlikely to achieve enrolment, and therefore its overall scientific objective, in a reasonable timeframe. This is due to challenges encountered in recruiting GA patients with a CFI rare variant genotype, which accounts for approximately 3% of the overall GA population. Hence the study has been adjusted to include Part 2 with a more recruitable population of GA patients with a broad genetic background. The modification of the study population is justified based on emerging data which strengthens the hypothesis that complement-targeted therapies have potential to treat a genetically broad GA population. With this amendment, the primary objective of the study remains unchanged; subjects will continue to be genotyped as part of the screening assessments for the study, and analysis of the effect of GT005 according to genetically defined subgroups (including the original population of CFI rare variants) is still planned

Protocol Version	Change	Justification
		• Part 2 of the study will evaluate the low ([redacted] vg) dose of GT005 in comparison to an untreated control arm. [redacted] Data generated from this study on the effect of the low dose in the broad genetic GA population will support the overall clinical data package being generated across the GT005 programme • The sample size of the study has been recalculated to account for the change in population to broad genetic GA patients and ensures that the study is statistically robust and can therefore achieve its scientific objective. The revised sample size of 202 provides 80% power to detect a statistically significant difference (alpha=0.05, 1-sided) between the low dose and untreated control arms, using a 2:1 randomisation ratio, assuming that there is a 25% difference in the treatment effect on GA lesion growth. Part 2 of the study will continue with a 2:1 randomisation ratio of active treatment to control, in order to minimise the number of untreated control subjects that are in the study
	• Updated Section 1.5 Study Rationale with more background on the broad genetic population in Part 2 and defined the study populations in Part 1 and Part 2 of the study	• For ease of review within the document, separate subheaders were introduced to provide further clarification on the differences in study design between Part 1 and Part 2 study populations
	• Updated Section 1.5.4 Dose Rationale and in the Synopsis to add Part 2 of the study design	• Clarified the low dose has been selected for Part 2 to gather supportive data on dose response for the overall GT005 clinical development programme
	• Updated the Synopsis and Section 3 Study Design to include Part 2, which randomises a broad GA population into a treatment arm (low dose, [redacted]) and untreated control • Updated Figure 1 study design to differentiate between Part 1 and Part 2 study design and clarified that enrolment in Part 1 should complete at each site first before enrolling subjects in Part 2	• Updated the study design with Part 2 to obtain more efficacy and safety data on low dose GT005 vs untreated control in a broad population. This study design now supports the overall development of GT005 across our GT005 clinical development programme since overall there has been less data captured from subjects who have been administered with the low dose • Due to a change in study design, Figure 1 has been updated to include Part 2 which has been broadened to enrol GA subjects with a broad genetic background and includes two treatment arms (treatment with low dose and untreated control).

Protocol Version	Change	Justification
	[redacted]	
	• Updated Study Objectives in Synopsis and Section 2 secondary [redacted] to be reported through Week 96	• Clarified the analysis timepoints for secondary [redacted] to be reported until the end of study
	[redacted]	
	• Updated the CFI rare variant genetic Inclusion Criterion 8 to relate to Part 1 of the study only	• Inclusion Criterion 8, CFI rare variant genotypes, will only be applicable to Part 1 of the study. Subjects in Part 2 will not require a genotyping subgroup classification to enter the study, as subjects with GA, secondary to AMD, irrespective of genotype will be allowed to enrol into Part 2
	• Updated Exclusion Criterion 1 to exclude those with Stargardt disease/retinal dystrophies	• Updated Exclusion Criterion 1 to align with other clinical study protocols and to formally exclude subjects with another retinal disease, other than GA, secondary to AMD. Previously, these subjects were excluded, however, it has now been made clear in the protocol's eligibility criteria
	• Updated Exclusion Criterion 11 to exclude investigational and approved GA products at study entry in the study eye or systemically	• In order to preserve the integrity of the clinical study, investigational and/or approved GA treatments have been excluded from use either systemically and in the study eye within the timeframe specified
	• Updated the Synopsis and Section 9 Statistical Methods in line with the change in sample size and study design	• The following sections were expanded/edited: Sample size determination, removed statement that all statistical tests will be at the nominal 0.05 one-sided level since no formal testing has been decided. More information and detail relating to the planned statistical analysis has been added to the protocol to provide evidence for maintaining the statistical integrity and robustness of the study design as currently approved by Health Authorities (HA)

Protocol Version	Change	Justification
	• Updated Section 5.6.2 Prohibited Medications to include guidance on the use of approved or investigational GA medications in subjects in the study to exclude from systemic and/or locally in the study eye up to the Week 48 primary endpoint and in the untreated group until the end of study	• In order to preserve the scientific integrity of the clinical study, guidance has been provided on the use of approved and investigational GA treatments
	• Clarification under Surgical Procedure of the Synopsis and Section 5.4 Dosing and administration that subretinal GT005 dosing will occur via one or more GT005 administration bleb(s).	• The text regarding the subretinal bleb dosing procedure for GT005 was clarified
	• Updated Section 3.4.1 Masking to separate the Masking criteria for Part 1 and Part 2 • Clarified that the Sponsor will be unmasked once the Week 48 database lock is reached. Provided guidance if an interim analysis is performed before or after the last subject completes their Week 48 visit	• Part 1 includes two doses of GT005 (high and low) and an untreated control arm; Part 2, includes one dose of GT005 (low dose) and an untreated control arm. Therefore, the masking criteria at a site level will be handled differently, i.e., dose-masked vs unmasked
	• Updated 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. • The masking status for Part 1 has not changed; for Part 2, the masking in this study has been updated due to the new study design [redacted]
	• Updated Section 5.5 Measures to Minimise Bias, to state that in Part 2, the Sponsor, Investigators, subjects, and study personnel performing clinical assessments will be ***unmasked*** to dose received, since only the low dose will be administered • Clarified that only the Part 1 study personnel will have an unmasked team to prepare GT005 for administration	• To maintain data integrity, due to a change in the Part 1 and Part 2 study design, it has been clarified that all study personnel will be unmasked to the dose received in Part 2, with two arms (treatment vs control) • No changes have been implemented, however clarified that Part 1 only study personnel will require an unmasked team for GT005 administration
	• Updated Section 3.4.2 [redacted]	• Since CFI rare variant subjects associated with low serum CFI are challenging to recruit, the updated study design will allow for more subjects with CFI rare variants to enter the study, [redacted]

Protocol Version	Change	Justification
	[redacted]	
	• Updated 7.4.2 Adverse Events and footnote 13 to clarify that any additional safety assessments may be collected to follow up on AEs	• In order to ensure subjects' safety and wellbeing in the study, Investigators could conduct additional safety tests at their clinical discretion to evaluate/monitor AEs. Accordingly, the text has been updated to define and provide further clarity to this original intent
	[redacted]	• [redacted]
		• [redacted]
	• Additional safety assessment with FAF at Week 5	• Included an additional safety assessment post GT005 delivery using FAF at Week 5
	• Included new text under footnote 1, Schedule of Assessments and Section 6.1.1, Screening Visit 1: Local or Surgical, to state that: other assessments may be performed at the investigator's discretion if the 8-week screening window passes • Added standard ophthalmic exam to the list of screening assessments that should be repeated for all subjects if the 8-week screening window passes • Additionally, included rescreening guidance ***within*** 8-weeks and ***after*** 8-weeks	• To ensure that we can collect this or any other assessment, if needed when the 8-week screening window passes, the text has been updated to allow this flexibility • For safety reasons added standard ophthalmic exam to the list of screening assessments that should be repeated for all subjects if the 8-week screening window passes • To ensure optimal operational management of the study, provided clarification that if a subject is rescreened within the 8-week screening period, the site staff need to repeat only the haematology/biochemistry, standard ophthalmic exam and visual acuity (BCVA and LLVA) assessment provided all other original results were acceptable Further, if a subject is rescreened after the 8-week screening period, all screening assessments should be repeated except for genotyping and serum CFI
	• Included new footnote 11 under Schedule of Assessments and in Section 6.1.9 Visit 6, [redacted] optional for all subjects treated with GT005	• [redacted]

Protocol Version	Change	Justification
	• Increased number of investigational sites from 40 to approximately 60	• Increased the number of global sites to approximately 60 to support recruitment in approximately 202 subjects
	Updated footnote 3 under the Schedule of Assessments and Section 6.1.3.2 Surgery Day 1 • Clarified that in the event GT005 dosing was deferred during surgery, the time from surgery may be rescheduled within 10 weeks of the original surgery date if agreed by the Sponsor Medical Monitor • 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)	• In the event that GT005 treatment is deferred, guidance has been provided
	• Updated recent information under Section 1.6.1.1 Risks associated with GT005 and ensured that the new information was also summarised under Section 1.6.3 Risk Benefit Analysis	• The Risks associated with GT005 Section has been aligned with the current version of the Investigator's Brochure (IB)
	• Updated Section 4.6 Discontinuation/Withdrawal and Section 4.3 Screen Failures and Replacements and provided an alternative to stopping participation entirely to subjects who were randomised to GT005 and do not want to receive treatment with GT005 and opt to have less assessments and data collected as part of the study	• To collect additional subject-level data and to preserve the integrity of trial data during the statistical analysis, additional guidance has been provided on the discontinuation/withdrawal from the study
	[redacted]	• [redacted]
	[redacted]	[redacted]
	• Updated Section 6.1.1 Screening guidance for subjects in Part 1 and Part 2. The genotyping assessment in Part 2 can be performed at the same time as other screening assessments	• To ensure optimal operational management of the study, subjects in Part 2 can have genotyping and all other screening assessments performed at the same visit (since subjects do not need to wait for genotyping confirmation for study entry)

Protocol Version	Change	Justification
	• Updated Section 6.1.5 Surgery Day 1 and 7.1 Demographic and Screening Assessments so subjects can provide consent to live-streaming of the surgery	• Subjects randomised to GT005 will be asked if they are willing to consent to have livestreaming of the intraocular surgical procedure for training and monitoring purposes, upon the subject providing consent
	• 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 • Signatory updated

Abbreviations: AEs=adverse events; AESI=adverse event of special interest; AMD=age-related macular degeneration; CFI=complement factor I; CNV=choroidal neovascularisation; CRC=Central Reading Centre; EU=European Union; FA=fluorescein angiography; GA=geographic Atrophy; IB=Investigational Brochure; ICF=informed consent form; IMP=investigational medical product; MHRA=Medicines and Healthcare products Regulatory Agency; OCT= optical coherence tomography; OCT-A= optical coherence tomography-angiography; PRL=preferred retinal locus; RoW=rest of world; RPE=retinal pigment epithelium.; SAEs=serious adverse events; USA=United States of America; V=version.

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 non-compliance will be documented.

PROTOCOL SYNOPSIS

SPONSOR:
Gyroscope Therapeutics

INVESTIGATIONAL MEDICINAL PRODUCT:
GT005: A recombinant 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:
EXPLORE: A Phase 2, outcomes assessor-masked, multicentre, randomised 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 age-related macular degeneration.

PROTOCOL NO:
GT005-02 (EXPLORE)

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

INVESTIGATOR STUDY SITES:
Approximately 60 study 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:
Age-related macular degeneration 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 GA [Chakravarthy 2010]. At the time of writing, 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]. Variants in genes of complement factors involved in the alternative pathway (Complement Factor H, Complement Factor I (CFI), Complement Factor B, and Complement component 3) have been found in AMD patients [Fritsche 2016]. These results suggest that mutations in these genes strongly correlate with the likelihood of developing AMD [Fritsche 2013; Fritsche 2016].

Study Population:
This study is composed of two parts: Part 1 and Part 2.
Part 1 of the protocol will selectively enrol subjects with GA who have either a CFI rare variant genotype associated with low serum CFI, or with a previously unreported CFI rare variant genotype that have tested to have low serum CFI.
Part 2 of the protocol will enrol subjects with GA across a broad, non-selective genetic background, irrespective of genotype, until approximately 202 subjects are randomised in the study overall.

Rare Variant Genetic Population (Part 1): Additional studies have found that rare genetic variants in CFI (defined by a minor allele frequency <1%) are associated with increased risk of advanced AMD, with one study showing that low serum CFI levels together with the presence of rare CFI variants is associated with an increased risk of development of advanced AMD [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] CFI rare variant genotypes previously associated with low serum CFI or subjects carrying an unreported CFI rare variant genotype that have tested to have a low serum CFI for study entry.

Part 1 of the study will close for enrolment once all appropriate approvals for protocol V6.0 are in place; subsequently, subjects with GA and a CFI rare variant genotype should then be entered into Part 2 of the study.

Broad Genetic Population (Part 2): 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].

Part 2 is designed to evaluate whether administering CFI will be effective in down-regulating a hyperactive complement system across all GA patients from a broad genetic population, irrespective of genotype, and if this intervention will have a therapeutic effect on disease progression. 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].

DOSE RATIONALE:

[redacted]

OBJECTIVES:

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

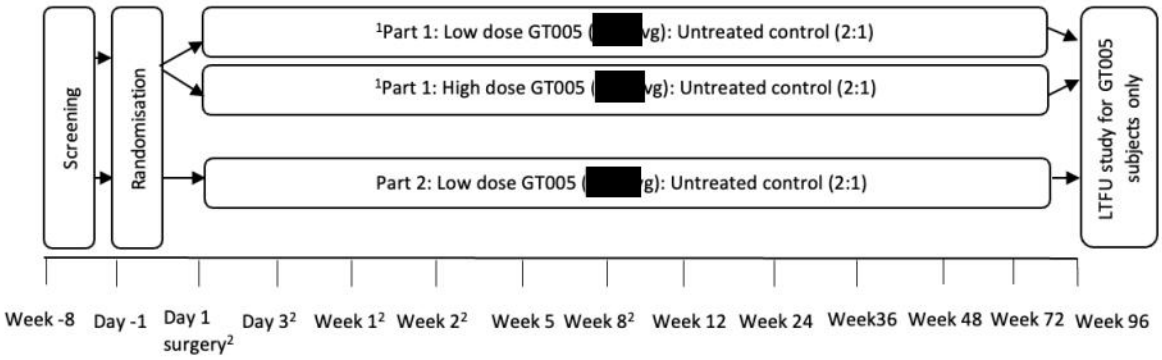
OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD	• The change from baseline to Week 48 in GA area as measured by fundus autofluorescence (FAF)
Secondary	
• To evaluate the effect of GT005 on the progression of GA in subjects with 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]

[redacted]

STUDY DESIGN:

This is a Phase 2, outcomes assessor-masked, 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 AMD. Approximately 202 subjects are planned to be randomised to GT005 or the untreated control group. Subjects who are screened, but not randomised, will be classified as Screen Failures and will be replaced. Subjects entering the study must have genotyping performed by a sponsor-approved laboratory, either through participation in a previous Gyroscope sponsored study or during the EXPLORE screening period.



[1]Investigational sites can open Part 2 for enrolment once all appropriate approvals for protocol V6.0 are in place (at which point Part 1 is considered closed for enrolment).
[2]GT005 allocated subjects only.

Figure 1: Study Design

Following consent, subjects will undergo ophthalmic and clinical assessments to determine eligibility for inclusion in the study. The consent process and screening assessments may occur at the subject's local or surgical investigative site. On confirmation of eligibility, subjects in Part 1, will be randomised to one of two dose groups (low dose [redacted]vg] or high dose [redacted] vg]). Within each part of the study, subjects will be allocated to GT005 or untreated control based on a 2:1 scheme [Figure 1]. Investigational sites can open Part 2 for enrolment once all appropriate approvals for protocol V6.0 are in place (at which point Part 1 is considered closed for enrolment. In Part 2, subjects will be randomised to one of two treatment groups (low dose [redacted]] or untreated control in a 2:1 scheme.

Determination of Study Eye:

In Part 1 and Part 2, 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 area of GA 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]. A permuted-block method will be used to obtain an approximately 2:1 ratio between the treatment group(s) and control within each part of the study within each stratum. [redacted]

Following randomisation, the Investigator will be informed of the subjects' allocated treatment assignment (i.e., treatment with GT005 or the untreated control group, but not the GT005 dose group) and the study eye selected. In Part 1, the Sponsor, Investigators, subjects, and study personnel performing clinical assessments will remain ***dose-masked*** to dose received for those randomised to GT005. In Part 2, the Sponsor, Investigators, subjects, and study personnel performing clinical assessments will be ***unmasked*** to the treatment arm (GT005 or untreated control) and therefore dose, since only the low dose will be administered. 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. [redacted]

Subjects screened at a local investigative site who are 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.

Subject consent, screening and confirmation of eligibility, and most follow-up visits will be conducted at either local or surgical investigative sites. Subjects allocated to GT005 will undergo subretinal surgery for the administration of GT005. [redacted] For women of childbearing potential, a second pregnancy test will be performed at Visit 2. GT005 is administered as a single-time subretinal injection into the study eye. [redacted]. 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; Table 2].

For each subject, the study duration will be up to 8 weeks of screening, followed by a 96-week study period. Screening assessments may be conducted over several days. All subjects will be assessed for the occurrence of AEs at each visit and will undergo functional visual and retinal imaging, anatomical assessments, and biological sampling as per the schedule of assessments see [Table 1; Table 2].

Subjects allocated to untreated control will be followed by the local or surgical investigative site. The pooled untreated control group will provide a reference group to the GT005 treatment groups.
Subsequent follow-up visits at Weeks 12, 24, 36, 48, 72, and 96 (Visits 6, 7, 8, 9, 10, and 11) will be conducted for both GT005 and untreated control subjects. GT005 treated subjects will have an additional visit at Week 8 (Visit 5). Visit 11 will be during Week 96 (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.

NUMBER OF SUBJECTS:

Approximately 202 subjects are planned, with subjects randomised to one of two GT005 dose groups (low dose [[redacted] vg] and high dose [redacted] vg]) in Part 1 and low dose in Part 2. Within each part of the study subjects will be allocated to GT005 or untreated control based on a 2:1 scheme.
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. 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)
4. Have GA lesion(s) total size between or equal to 1.25mm^2 to 17.5mm^2 in the study eye
5. The GA lesion(s) 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:
    a. Non-exudative/sub-clinical fellow eye CNV identified at Screening, or
    b. Known history of fellow eye CNV with either ≥2 years since diagnosis or with no active treatment required in 6 months prior to Screening
7. Have a BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent) or better, using ETDRS charts, in the study eye
8. **Part 1 Only:** Subjects carrying a CFI rare variant genotype (minor allele frequency of ≤ 1%) previously associated with low serum CFI or subjects carrying an unreported CFI rare variant genotype that have tested to have a low serum CFI
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. 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. Subjects who have a clinical diagnosis of Stargardt Disease or other retinal dystrophies, confirmed by the central reading centre
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 Screening (Visit 1). Yttrium aluminium garnet capsulotomy is permitted if performed >10 weeks prior to Visit 1
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 in the study eye; uncontrolled intraocular pressure (IOP) despite the use of more than two topical agents; a history of glaucoma-filtering or valve surgery
8. Axial myopia of greater than -8 dioptres in the study eye
9. 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
10. Have a contraindication to the specified protocol corticosteroid regimen
11. Have received any investigational and/or approved product(s) 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 in the study eye or systemically
12. Have received a gene or cell therapy at any time
13. Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant
14. 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

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 room 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 one or more GT005 administration bleb(s). [redacted] The bleb(s) 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 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.

REFERENCE TREATMENT:

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

STATISTICAL METHODS:

Sample Size and Statistical Power

Untreated control mean GA change at 48 weeks was assumed to be 2.1 mm^2 with SD=1.3 mm^2. Up to ~10–12% of subjects are expected to discontinue treatment and not provide the target 48 week observation. [redacted]

Analysis Sets

The Full Analysis Set (FAS) will include all subjects who are randomised to GT005 or untreated control. A 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 endpoint, change from baseline to Week 48 in GA area, will be compared between treatments via least squares means from analysis of covariance (ANCOVA). Details of the model specifications and data imputation approaches will be specified in the Statistical Analysis Plan (SAP). Other continuous efficacy endpoints will be analysed similarly using mixed model repeated measures (MMRM).

Categorical and binary endpoints will be summarised by counts and percentages by dose. No statistical inferential testing is planned for all endpoints since this is an exploratory Phase 2 study.

[redacted].

Safety Assessments

Safety evaluations include AEs, ophthalmic imaging and examinations, BCVA and Low Luminance Visual Acuity for LLD (ETDRS) score (assessed as both an efficacy and safety endpoint), vital signs, laboratory safety (biochemistry and haematology), and [redacted]

AEs will be summarised in two parts: systemic events and ocular events. For systemic events, data will be displayed according to treatment received (untreated, low dose [redacted vg] and high dose [redacted vg]). Ocular events will be displayed according to treatment allocation (including GT005 dose group 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, intra-ocular pressure, etc.) and BCVA scores, will be summarised in the same manner as ocular efficacy variables, dependant on data type.

Interim Analyses

The analysis based on the Week 48 data will be the primary efficacy analysis for this study.

The database including all Week 48 data will be locked once all enrolled subjects from Part 1 and Part 2 have completed the Week 48 visit or terminated the study prior to Week 48. 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.

Additional interim analyses may be considered to help inform internal development decision points for GT005, in which case the details will be pre-specified in the SAP prior to conducting the analysis.

MONITORING COMMITTEES

Data Monitoring Committee

The Data Monitoring Committee (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 Independent Statistics Centre (ISC) as per the DMC Charter to ensure safety of the subjects. Only the DMC and ISC will be unmasked to Part 1 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 and to perform the clinical outcome analyses.

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

Location	Local or Surgical Site		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]	Day 1 (Dosing) Surgery	Day 2 Post-surgery[3]	Day 3	Week 1	Week 2	Week 5	Week 8[4]	Week 12	Week 24	Week 36	Week 48	Week 72	Week 96/EoS	
Window	-8 weeks					+ 1 day	± 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[5]															
Demographics	X																
Medical/Surgical history	X		X														
Pregnancy Test[6]	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[7]	X																
Genotyping[7]	X																
[redacted]																	
Surgery and dosing of GT005				X													
[redacted]																	
Adverse events[13]	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												
Ophthalmic examination	X				X		X		X	X	X	X	X	X	X	X	X
Pre-surgical ocular safety check			X[14]														
CFP	X								X					X	X	X	X
FAF	X								X		X	X	X	X	X	X	X
OCT-Macula	X				X		X		X		X	X	X	X	X	X	X
[redacted]																	

Location	**Local or Surgical Site**		**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[3]	**Day 3**	**Week 1**	**Week 2**	**Week 5**	**Week 8[4]**	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 72**	**Week 96/EoS**	
Window	**-8 weeks**					**+ 1 day**	**± 3 days**	**±3 days**	**±7 days**	**+3/-7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	
OCT-A	X[15]						X[16]										
Fluorescein angiography	X[15]						X[16]										
[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[19]														
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; FA=fluorescein angiography; FAF=fundus autofluorescence; FRI=functional reading independence; LLD=low luminance difference; LLVA= low luminance visual acuity; MAIA=macular integrity assessment; MNRead=assessment of reading performance; OCT=optical coherence tomography; Tel=telephone; VFQ=visual function 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 8 week screening period has elapsed, standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA should be repeated prior to surgery; other assessments may be performed at the investigator's discretion. If a subject is rescreened ***within*** 8 weeks of the original screening visit date, 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 ***after*** 8 weeks of the original screening visit date, all screening assessments should be repeated with the exception of genotyping and serum CFI.
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. In the event that GT005 administration is deferred during the surgical procedure (e.g. due to an adverse event) the administration surgery may be rescheduled within 10 weeks of the original surgery date 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.
4. Study assessments at Week 8 may be conducted at +3/-7 days of the study visit.
5. Randomisation will occur following confirmation of eligibility; subjects will be informed via telephone call of the randomisation outcome.
6. Only for women of child-bearing potential.
7. To be completed only if not previously performed at a Sponsor-approved laboratory.

[redacted]

Location	Local or Surgical Site		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]	Day 1 (Dosing) Surgery	Day 2 Post-surgery[3]	Day 3	Week 1	Week 2	Week 5	Week 8[4]	Week 12	Week 24	Week 36	Week 48	Week 72	Week 96/EoS	
Window	-8 weeks					+ 1 day	± 3 days	±3 days	±7 days	+3/-7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	

[redacted]

12. To be collected only if termination occurs after Visit 4 (Week 5) and before Visit 8 (Week 36).
13. AEs should be captured from the date of signing the informed consent form. Additional assessments may be conducted, as needed, to allow for safety assessment.
14. 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.
15. CNV assessment at screening/prior to surgery 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.
16. OCT-A and/or FA may be performed during the study period if clinically indicated, for example, if a subject converts to wet AMD.

[redacted]

19. 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									Early Termination Visit (ALL)
Visit Number	**1**	**Tel Call**	**Tel Call**	**6**	**7**	**8**	**9**	**10**	**11**	
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/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			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]						
Fluorescein angiography	X[6]			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; FA=fluorescein angiography; FAF=fundus autofluorescence; FRI=functional reading independence; LLD=low luminance difference; LLVA=low luminance visual acuity; MAIA=macular integrity assessment; MNRead=reading performance; OCT=optical coherence tomography; Tel=telephone; VFQ=visual function 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 8-week screening period has elapsed, standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA should be repeated prior to surgery; other assessments may be performed at the investigator's discretion. If a subject is rescreened ***within*** 8 weeks of the original screening visit date, 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 ***after*** 8 weeks of the original screening visit date, 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 the date of 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 FA. Further details are provided in the Central Imaging Manual.
7. OCT-A and/or FA may be performed during the study period if clinically indicated, for example, if a subject converts to wet AMD.

[redacted]

1. BACKGROUND INFORMATION

A full description of the indication, investigational medicinal product (IMP), preclinical and clinical data available for GT005 is provided in the Investigator's 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 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 Preclinical Studies

[redacted]

[redacted]

[redacted]

A detailed description of the preclinical data is provided in the IB.

1.4 Clinical Studies

A single first-in-human study evaluating the safety, dose response and efficacy of three doses of GT005 administered by subretinal injection to subjects presenting with GA due to AMD is ongoing.

1.5 Study Rationale

1.5.1 The Complement Cascade

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]. Variants in genes of complement factors involved in the alternative pathway (Complement Factor H, CFI, Complement Factor B, and Complement component 3 [C3]) have been found in AMD patients [Fritsche 2016]. The results of a number of genome-wide association studies suggest that mutations in these genes strongly correlate with the likelihood of developing AMD [Fritsche 2013; Fritsche 2016]. Additional studies have found that some rare genetic variants of CFI (defined by a minor allele frequency <1%) are associated with increased risk of advanced AMD, with one study showing that low serum CFI levels together with the presence of rare CFI variants is associated with an increased risk of development of advanced AMD [Seddon 2013; Kavanagh 2015; Geerlings 2017].

1.5.2 Rare Variant Genetic Population (Part 1)

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, reducing the progression of the disease. The subset of GA patients with CFI rare variant genotype associated with a low serum CFI may demonstrate a larger response to treatment that supplements CFI locally, correcting the effects of their complement gene mutation. AAV2 vector-based CFI gene transfer (GT005) provides a sustained expression of human CFI in AMD

patients' eyes and is expected to result in down-regulation of the alternative complement pathway.

Part 1 will only consider CFI rare variant genotypes previously associated with low serum CFI or subjects carrying an unreported CFI rare variant genotype that have tested to have a low serum CFI for study entry.

Part 1 of the study will close for enrolment once all appropriate approvals for protocol V6.0 are in place; subsequently, subjects with GA and a CFI rare variant genotype should then be entered into Part 2 of the study.

1.5.3 Broad Genetic Population (Part 2)

Part 2 of the EXPLORE Phase II clinical study aims to assess the safety and efficacy of GT005 in a broad population of GA subjects, regardless of genotype.

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]. Rare, functionally damaging variants in CFH, CFB and C3 strongly predispose to AMD [Raychaudhuri 2011; Seddon 2013; Zhan 2013; Saksens 2016]. 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].

Part 2 is designed to evaluate whether administering CFI will be effective in down-regulating a hyperactive complement system across all GA patients from a broad genetic population and if this intervention will have a therapeutic effect on disease progression. 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].

1.5.4 Dose Rationale

[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]. It has been demonstrated that normal levels of CFI in plasma and vitreous humor are

28,366 and 691 ng/mL, respectively [Mandava 2019].

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, the surgical delivery of GT005, and study procedures.

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,

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 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, 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]

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]

[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. GT005 is considered to pose negligible risk to humans, animals, and the environment.

[redacted]

Retinal Pigment Epithelium (RPE) Changes
Pigmentary changes have been noted in the RPE of some subjects receiving GT005 via subretinal delivery (Refer to the IB for further information). These changes are limited to the bleb area and in most cases were first seen at Week 12 and are identifiable on FAF. In a minority of cases an area of depigmentation can also be seen on colour fundus photography (CFP).

1.6.1.2 Risks Associated with the Surgical Procedure and Study Procedures

The surgical technique employed for this clinical study has been developed for and successfully used for the choroideremia subretinal gene therapy clinical studies [MacLaren 2014; Xue 2017]. Risk mitigation 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 adverse events (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 GT005 study and assessed as likely to require cataract surgery during the 12-month study period will 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 48 visit.

Intraocular pressure elevation is a risk associated with vitrectomy procedures [Chang 2006] and periocular or topical steroids [Kersey 2006]. In publicly available safety data, voretigene neparvovec (Luxturna®), had reports of elevation in intraocular pressure in 8 of 81 eyes treated (10%). Subjects will have intraocular pressure (IOP) checked at every visit to ensure adequate monitoring and therapies 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 visual loss.

1.6.3 Risk Benefit Analysis

GT005 is currently being evaluated in an ongoing Phase 1/2 clinical study and therefore the potential risks are based on clinical data from an ongoing dose escalation safety study, preclinical data, and available scientific knowledge of AAV2 vectors carrying different transgenes for the treatment of various retinal conditions without significant AEs related to these Drug Products [MacLaren 2014; Russell 2017; Heier 2017; Voretigene Neparvovec FDA ACM 2017].

[redacted]

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 further developed and successfully used 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 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 safety and efficacy (anatomical and functional visual outcomes) of two doses of GT005 in genetically defined subjects with GA due to AMD.

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD	• The change from baseline to Week 48 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 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 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 functioning questionnaire-25 (VFQ-25) through Week 96
[redacted]	

3 STUDY DESIGN

3.1 Study Overview

This is a Phase 2, outcomes assessor-masked, multicentre, randomised 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 AMD. Approximately 202 subjects are planned to be randomised to GT005 or the untreated control group. 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 a previous Gyroscope sponsored study, or during the EXPLORE screening period. Data from subjects screened in another Gyroscope sponsored study at the same investigative site as EXPLORE 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 EXPLORE, they will be classed as Screen Failures for this study and may be considered for entry into another Gyroscope sponsored study.

Following consent, subjects will undergo ophthalmic and clinical assessments to determine eligibility for inclusion in the study. The consent process and screening assessments will occur at either the subject's local or surgical investigative site. A proportion of the study sites will be designated as centralised surgical sites.

On confirmation of eligibility, subjects in Part 1, will be randomised to one of two dose groups (low dose [vg] or high dose vg]). Within each part of the study, subjects will be allocated to GT005 or untreated control based on a 2:1 scheme [Figure 1]. Once Part 1 enrolment is completed, and the last active subject completes screening and either screen fails or is randomised, then Part 2 can commence. In Part 2, subjects will be randomised to one of two treatment groups (low dose [or untreated control) in a 2:1 scheme.

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 area of GA 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. A permuted-block randomisation method will be used to obtain an approximately 2:1 ratio between GT005 and the untreated control arms for each dose group within each stratum [Figure 1].

Following randomisation, the Investigator will be informed of the subject's allocated treatment (i.e., treatment with GT005 or the untreated control group) and the study eye selected. 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 parameters 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, subjects, investigators, 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 at centralised surgical sites for the administration of GT005. For women of child-bearing potential a second pregnancy test will be performed at Visit 2. GT005 is administered as a single-time subretinal injection into the study eye. [redacted] Following the subretinal injection, GT005 subjects may be maintained in the clinic overnight up to 24 hours to assess any AEs resulting from the surgery. 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; Table 2].

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. All subjects will be assessed for the occurrence of AEs at each visit and will undergo functional visual and retinal imaging, anatomical assessments, and biological sampling as per the schedule of assessments [Table 1; Table 2].

Subjects allocated to untreated control will be followed by the local investigative or surgical site. The pooled untreated control group will provide a reference group to the GT005 treatment groups.

[redacted]

Subsequent follow-up visits at Weeks 12, 24, 36, 48, 72, and 96 (Visits 6, 7, 8, 9, 10, and 11) will be conducted for both GT005 and untreated control subjects at the local investigative or surgical sites. Visit 11 will be during the Week 96 (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]

This study includes an untreated control group for comparison.

3.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) will perform safety reviews of unmasked data, as defined in the DMC Charter, to ensure safety of the subjects and to inform the Sponsor on efficacy outcome trigger criteria, to inform business strategy outside of this clinical study.

The DMC is an independent committee that will be comprised 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 and to perform the clinical outcome analyses.

No DMC member will be an Investigator in the study. Full details regarding the DMC mission and content, of the DMC reviews are detailed in the DMC Charter and 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 ***dose-masked*** to the GT005 dose group (high dose [redacted] and low dose [redacted] vg) assigned in Part 1. The Sponsor will be unmasked once the Week 48 database lock is reached. Alternatively, if an interim analysis is performed, the Sponsor may be unmasked to Part 1 data if the interim occurs after the last subject in Part 1 completes their Week 48 visit, and the clinical database is frozen for that interim analysis. Should an interim analysis be performed prior to all Part 1 subjects completing the Week 48 visit, this will be conducted by a separate Sponsor team, members of which will have no site level interactions or study-related engagement with the rest of the study team. In all instances, masking to the doses in Part 1 will be maintained at the site level (subjects, masked site personnel and masked monitors) until the end of the study.

In Part 2, given only one dose (low dose [redacted] vg) is administered in the study, the Sponsor, Investigator, the site personnel, and the subject will be ***unmasked*** to the treatment arm (GT005 or untreated control).

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]

In Part 1, unmasked study site personnel will be assigned the responsibility of preparing the GT005 solution for administration, which for the lower dose of [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

Subjects in Part 1 will be randomised to one of two dose groups; low dose ([redacted] vg) or high dose [redacted] vg). Subjects in Part 2 will be randomised to one of two treatment groups; low dose [redacted] vg) or untreated control.

[redacted]

A permuted-block randomisation method will be used to obtain an approximately 2:1 ratio between treatment with GT005 and the untreated control group(s) for each dose group within each stratum.

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 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 receiving GT005 and those allocated to untreated control, will be followed for 96 weeks. After the final follow-up visit or early termination 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 (AESIs) 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, or
- 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) 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)
4) Have GA lesion(s) total size between or equal to 1.25mm^2 to 17.5mm^2 in the study eye
5) The GA lesion(s) 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:
    a. Non-exudative/sub-clinical fellow eye CNV identified at Screening, or
    b. Known history of fellow eye CNV with either ≥2 years since diagnosis or with no active treatment required in 6 months prior to Screening
7) Have a BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent) or better, using ETDRS charts, in the study eye
8) **Part 1 Only:** Subjects carrying a CFI rare variant genotype (minor allele frequency of ≤1%) previously associated with low serum CFI or subjects carrying an unreported CFI rare variant genotype that have tested to have a low serum CFI
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. 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) Subjects who have a clinical diagnosis of Stargardt Disease or other retinal dystrophies, confirmed by the central reading centre
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 Screening (Visit 1). Yttrium aluminium garnet capsulotomy is permitted if performed >10 weeks prior to Visit 1

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 in the study eye; 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 dioptres in the study eye

9) 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

10) Have a contraindication to specified protocol corticosteroid regimen

11) Have received any investigational and/or approved product(s) 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 in the study eye or systemically

12) Have received a gene or cell therapy at any time

13) Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant

14) 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

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/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.

Subjects who are withdrawn from the study after randomisation will not be replaced. The reason for the subject's withdrawal from the study will be recorded in the electronic case report form (eCRF).

Subjects who are randomised to GT005 treatment but do not subsequently get dosed, should be offered the option to continue in the study following the same visit schedule as those who are allocated to the untreated control arm [Table 2]. The reason for not receiving GT005 should be recorded in the eCRF.

4.4 Randomisation Criteria

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 or 2 years postmenopausal) 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, subjects should be made aware that once surgery has taken place, they can withdraw from the study but cannot withdraw from the study treatment.

If appropriate, subjects who are considering withdrawing from the study should be offered the option to continue in the study with less intensive assessments, as an alternative to complete discontinuation from the study. If the subject is willing to continue with less intensive visits, this should be recorded in the subject's medical record and the eCRF, and the following minimum data should be collected at clinic visits or via telephone/email contact (preferably according to the study visit schedule):

- New treatments and/or change in concomitant treatments
- Adverse Events

If the contact is performed via telephone, this should ideally be done directly with the subject, or alternatively with another person pre-designated by the subject to convey information on their behalf.

If agreed between the subject and the Investigator, additional data may also be collected at these visits, according to the study visit schedule and with consideration to the key primary and secondary endpoints for the study.

If the subject completely withdraws from the study, the reason for discontinuation/withdrawal of subjects must be determined by the Investigator and recorded in the subject's medical record and in the 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
- Study cancellation by the Sponsor

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). As 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, subject to consent, be enrolled in a separate long-term follow-up study (ORACLE). The long-term follow-up study will evaluate the long-term safety and durability of GT005 after the final follow-up visit at Week 96 or early termination visit. 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 is 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.

For Part 1, 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. Masking to the doses in Part 1 will be maintained at the site level (subjects, masked site personnel and masked monitors) until the end of the study. For Part 2, designated unmasked study member(s) is (are) not required.

All expired GT005 should be recorded in the accountability records and will be destroyed locally, as per local guidelines once final accountability is completed. Details regarding the handling and preparation of GT005 are detailed in the Pharmacy Manual.

5.2 Formulation, Appearance, Packaging and Labelling (include comparator information)

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 will be labelled in accordance with the appropriate Competent Authority regulations.

[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; low dose ([redacted] vg) and high dose ([redacted] vg) in Part 1; and low dose [redacted] vg) in Part 2.

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 a 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 detailed procedure is described in the Surgical Manual.

Subjects allocated to GT005 treatment are injected with GT005 across a minimum of one or more bleb(s) following the procedure below:

[redacted]

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

5.5 Measures to Minimise Bias: Randomisation and Masking

This is an open label, outcomes assessor-masked study. In Part 1, the Sponsor, Investigators, subjects, study personnel involved in the study will remain ***dose-masked*** to those randomised to GT005.

In Part 2, the Sponsor, Investigators, subjects, and study personnel performing clinical assessments will be ***unmasked*** to dose received, since only the low dose will be administered.

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.

For Part 1 only, 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., consent, 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]

[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) and Section 5.6.2 Prohibited Medication. If the fellow (non-study) eye requires treatment for GA, it may be treated at the discretion of the investigator. Fellow eye treatment will be captured in the eCRF. The fellow eye must be monitored according to routine clinical practice and AEs captured in the eCRF.

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.

The treatments displayed in Table 3 below are not allowed after Visit 1 (screening).

Table 3: Prohibited Medications for Study Eye Only

Medication	Prohibition period for GT005 arm	Prohibition period for untreated control arm	Action taken
Investigational GA medication	Week 96	Week 96	Record in eCRF and continue with study visits until end of study
Approved GA medication	Week 96	Week 48	Record in eCRF and continue with study visits until end of study

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 (see Section 5.6.1).

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 received 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 also approved 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 all 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 Site)

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 EXPLORE 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 EXPLORE 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.

For Part 1 only: Where prior genotyping has been performed on subjects as aforementioned, and the subject is shown to carry a CFI rare variant that meets inclusion requirements, then the complete screening visit (Visit 1) can take place.

If a subject has been genotyped at an alternative laboratory and shown to carry a CFI rare variant that meets inclusion requirements, then the complete screening visit (Visit 1) can take place, however an additional sample for confirmation of genotype must be taken at this time to confirm the finding. A separate informed consent form (ICF) will be used to obtain permission to perform the confirmation of genotype. This consent may be performed and obtained remotely, if required. The subject may not continue past Visit 1 until genetic confirmation has been obtained.

For those subjects who have not previously been genotyped, and who fulfil Inclusion Criteria 1, 2, and 3, consent for genotyping and a genotyping sample should be obtained prior to performing any other screening assessments (Visit 1). A separate ICF will be used to obtain permission to perform the genotyping. This consent may be performed and obtained remotely, if required. The subject can then proceed to perform the remaining screening assessments once genetic confirmation has been obtained.

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

Screening Assessments

For Part 1 only (as described above), genotyping may be performed first and only subjects that are found to have the genetic variant of interest will be invited back to complete the remaining screening assessments.

For Part 2 only, genotyping is performed as part of the overall screening assessments, since all subjects are genetically eligible to participate in this study.

The screening assessments (Visit 1) will determine the full 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.

The following screening assessments are required for ALL subjects:

- Demographics
- Medical/surgical history
- Concomitant medication
- Genotyping (only required if not already available from a Sponsor-approved laboratory. Genotyping results will be received to confirm eligibility prior to other screening activities in Part 1 only)
- Pregnancy test (for women of child-bearing potential only)
- AEs
- Vital signs
- Biochemistry/haematology
- Serum CFI level (only required if not already available from a Sponsor-approved laboratory)
- [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*
- Low luminance visual acuity (LLVA) using ETDRS for LLD*
- MNRead
- VFQ-25
- FRI Index

*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, haematology/biochemistry, standard ophthalmic exam and BCVA/LLVA should be repeated; other assessments may be performed at the investigator's discretion.

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: pre-surgery, surgery, and post-surgery assessments.

6.1.3.1 Pre-surgery (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
- Vital signs
- AEs
- [redacted]
- [redacted]
- Pre-surgical ocular safety check to verify there are no new ocular adverse events 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 administration surgery may be rescheduled within 10 weeks of the original surgery date 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 assessments are required during surgery:

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

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

[redacted]

6.1.3.3 Post-surgery – Day 2 (Surgical Site)

The following assessments are required one day post-surgery:

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

6.1.4 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

6.1.5 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)

6.1.6 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

6.1.7 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 local site Investigator and the Surgeon.

Subjects allocated to untreated control will receive a telephone call from their local investigative site 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/haematology
- [redacted]
- Ophthalmic examination
- OCT macula
- [redacted]
- BCVA using ETDRS
- CFP
- FAF
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.8 Visit 5, Week 8 (Local or Surgical Site)

Visit 5 (Week 8) assessments listed below will only apply to subjects randomised to GT005:

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

- [redacted]

6.1.9 Visit 6, Week 12 (Local or Surgical Site)

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

- Concomitant medication
- [redacted]
- AEs
- [redacted]
- Biochemistry/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]

6.1.10 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/haematology
- [redacted]
- [redacted]
- Ophthalmic examination
- FAF

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

6.1.11 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
- MNRead
- VFQ-25
- FRI Index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.12 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/haematology
- [redacted]
- [redacted]
- [redacted]
- AEs
- Ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- MNRead
- VFQ-25
- FRI Index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.13 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/haematology
- AEs
- Ophthalmic examination

- CFP
- FAF
- OCT macula
- [redacted]
- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- MNRead
- VFQ-25
- FRI Index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

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

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

- Concomitant medication
- Vital signs
- Biochemistry/haematology
- [redacted]
- [redacted]
- [redacted]
- AEs
- Ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]

- [redacted]
- BCVA using ETDRS
- LLVA using ETDRS for LLD
- MNRead
- VFQ-25
- FRI Index
- OCT-A and/or FA if clinically indicated (if a subject converts to wet AMD)
- [redacted]

6.1.15 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 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 Gyroscope sponsored study or during the EXPLORE screening period. Informed consent will include permission for genotyping (genotyping and serum CFI evaluation are not required for subjects who have these from another Gyroscope study) and a consent from each subject or legal representative to enrol into EXPLORE 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 EXPLORE 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 EXPLORE, 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 ICF will be given to the participant. The original signed form 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, sex, at baseline 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

For those subjects who have not previously been genotyped, and who fulfil Inclusion Criteria 1, 2, and 3, consent for genotyping and a genotyping sample should be obtained prior to performing any other screening assessments (Visit 1). Where necessary, and to help fulfill this requirement, Visit 1 can occur over a number of days.

7.2 Concomitant Medication [redacted]

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, intraocular pressure 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]. Intraocular pressure 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; the CRC will transfer the data to the data management group and/or Independent Statistics Centre (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 ([redacted] Macula)

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 images 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 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 images 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 which is an eligibility exclusion criterion. Other imaging modalities as described in the Central Imaging Manual may also 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 nanometres, 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]

[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 Snellen result is >2 lines (BCVA equivalent to 10 letters), worse than the previous BCVA ETDRS score, then a BCVA with ETDRS assessment must be repeated. If the BCVA with EDTRS results is ≤2 lines worsened compared to the previous BCVA with ETDRS, record the subject's 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 and 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. 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. The LLD is calculated as the difference between BCVA and LLVA.

7.3.12 Reading Performance

Monocular (study eye separate from contralateral eye) Reading Speed will be assessed by the Minnesota Low-Vision Reading Test (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

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 (NEI-VFQ) [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. 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 [Appendix 17.5]. 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) is to be measured in triplicate after 5 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. AEs are collected from the time written informed consent is provided until end of 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 menarche 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 4]. 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 4: 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)*		

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

[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 EXPLORE screening period. [redacted] Justification and definition of rare variant genotypes (minor allele frequency of ≤ 1%) previously associated with low serum CFI will be provided in the document 'Definition of CFI Genotype Eligibility for Clinical Studies for GT005'.

[redacted]

[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

An 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.

[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 Events of Special Interest

All SAEs and AESIs, regardless of treatment group or suspected relationship to IMP or surgical procedures, 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 form.

Any 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.

Any AE/SAE with a suspected causal relationship to IMP administration occurring at any other time after completion of the study must be promptly reported.

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/AESIs 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, where possible, sufficient information should be 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, 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 subjects withdraw from the study due to an AE/SAE/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/IECs/IRBs/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

The mean GA change at 48 weeks in the untreated control group was assumed to be 2.1 mm^2 as was reported by [Holz 2018], with SD=1.3 mm^2.

The following hypotheses are considered:

$$H0_L: \mu_L - \mu_C = 0, HA_L: \mu_L - \mu_C < 0$$

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

Where μ_L, μ_H and μ_C represent the unknown true mean GA change on FAF at 48 weeks in the GT005 low dose [redacted], GT005 high dose [redacted] and pooled untreated control, respectively.

[redacted] Including the additional subjects that are already randomised to the high dose group (approximately 10 subjects) in Part 1, the overall sample size is approximately 202.

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 the GT005 or control group and provide at least one post baseline observation.

9.3 Significance Testing and Estimations

Type 1 error (alpha) is set at 0.05 one-sided and estimates of outcome parameters will be accompanied by 90% confidence intervals to be consistent with the Type 1 error level. No multiplicity adjustment will be applied since this is an exploratory study.

9.4 Statistical/Analytical Methods

9.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics including age, race, ethnicity, sex, as well as baseline GA lesion size, will be summarised with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total for each defined analysis population.

9.4.2 Efficacy Assessments

The primary endpoint, change from baseline to Week 48 in GA area, will be compared between treatments via least squares means from analysis of covariance (ANCOVA). The primary estimand will focus on the effect of different doses of GT005 on GA change on FAF at Week 48 and account potential unfavourable effects of GT005. The primary estimand includes the following components:

- Population: subjects with GA secondary to AMD
- Variable: Change from baseline in GA lesion size on FAF at Week 48

- Treatment: the randomised treatment of the investigational therapy GT005
- Intercurrent events: defined in Table 5 below:

Table 5: Intercurrent events and corresponding primary data handling strategies

Intercurrent event	Data handling strategy
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Details of the model specifications and further details on data imputation approaches will be described in the SAP. Other continuous efficacy endpoints will be analysed similarly using mixed model repeated measures (MMRM). [redacted]

Categorical and binary endpoints will be summarised by counts and percentages by dose. No statistical inferential testing is planned for any endpoint since this is an exploratory Phase 2 study.

9.4.3 Safety Assessments

Safety evaluations include AEs, ophthalmic imaging and examinations, BCVA (ETDRS) score (assessed as both an efficacy and safety endpoint), 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 received (low dose [vg], high dose [vg], and untreated). Ocular events will be displayed according to treatment allocation (including GT005 dose group) and study eye (study eye and contralateral eye).

All AEs (overall, by seriousness, by severity, by relationship) recorded throughout the study will be reported following classification according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

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

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

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9.4.5 Interim Analyses

The analysis based on the Week 48 data will be the primary efficacy analysis for this study. The database including all Week 48 data will be locked once all enrolled subjects have completed the Week 48 visit or terminated the study prior to Week 48. 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.

Additional interim analyses may be considered to help inform internal development decision points for GT005, in which case the details will be pre-specified in the SAP prior to conducting the analysis.

9.4.6 Data Monitoring Committee

The DMC will review the unmasked data as defined in the DMC Charter to ensure safety of the subjects and to inform the Sponsor on efficacy outcome trigger criteria to inform business strategy outside of this clinical study. There is no intention to stop this study for an early efficacy conclusion, so there is no impact of the Type 1 error. An ISC will conduct these interim analyses. The DMC and ISC will be unmasked to study data during the conduct of the study.

The DMC is an independent committee that will be comprised 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.

9.4.7 Handling missing data

Missing or censored data will be handled in accordance with the handling data strategy for intercurrent events as described in Table 5. The details of the statistical approaches for missing and/or censored data imputation will be described in the SAP and may include additional missing 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, 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 system 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 is always 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 investigative 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/institution should have written and dated approval/favourable opinion from the IEC/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/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/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/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

13.2 Subject Information and Consent

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. Written informed consent will be obtained from each subject before any study related procedures or assessments are performed.

The Sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the Sponsor, and the IEC/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/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 requested by FDA 21 CFR Part 54.

14.5 Insurance, Indemnity and Compensation

[redacted]

For covered clinical studies (see 21CFR54), the Investigator will provide the Sponsor with financial information required to complete Form FDA 3454. 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 or 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 or 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 eCRF. 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 AREDS 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 10x 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:

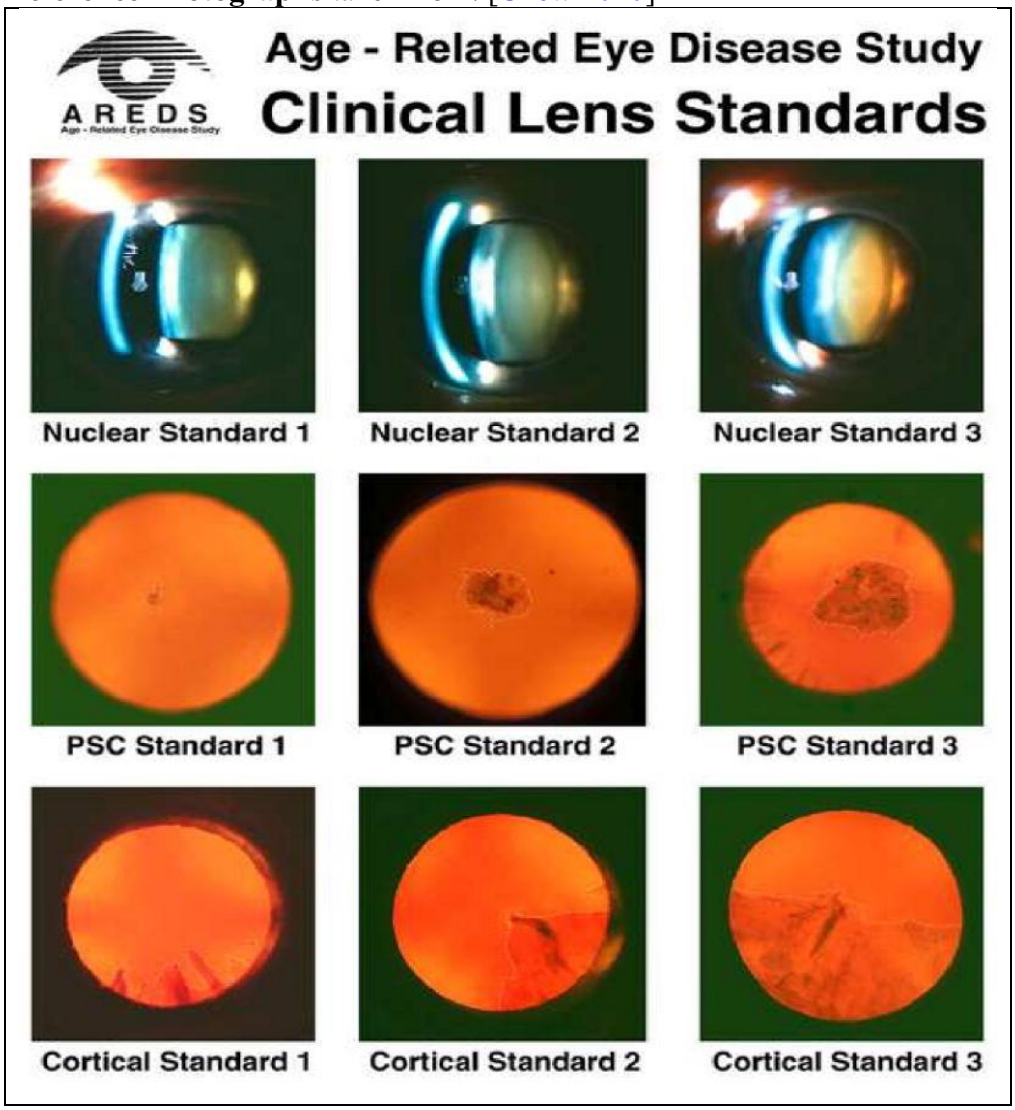
I. 0-2% (grade 0)

II. 2-20% (grade 1)

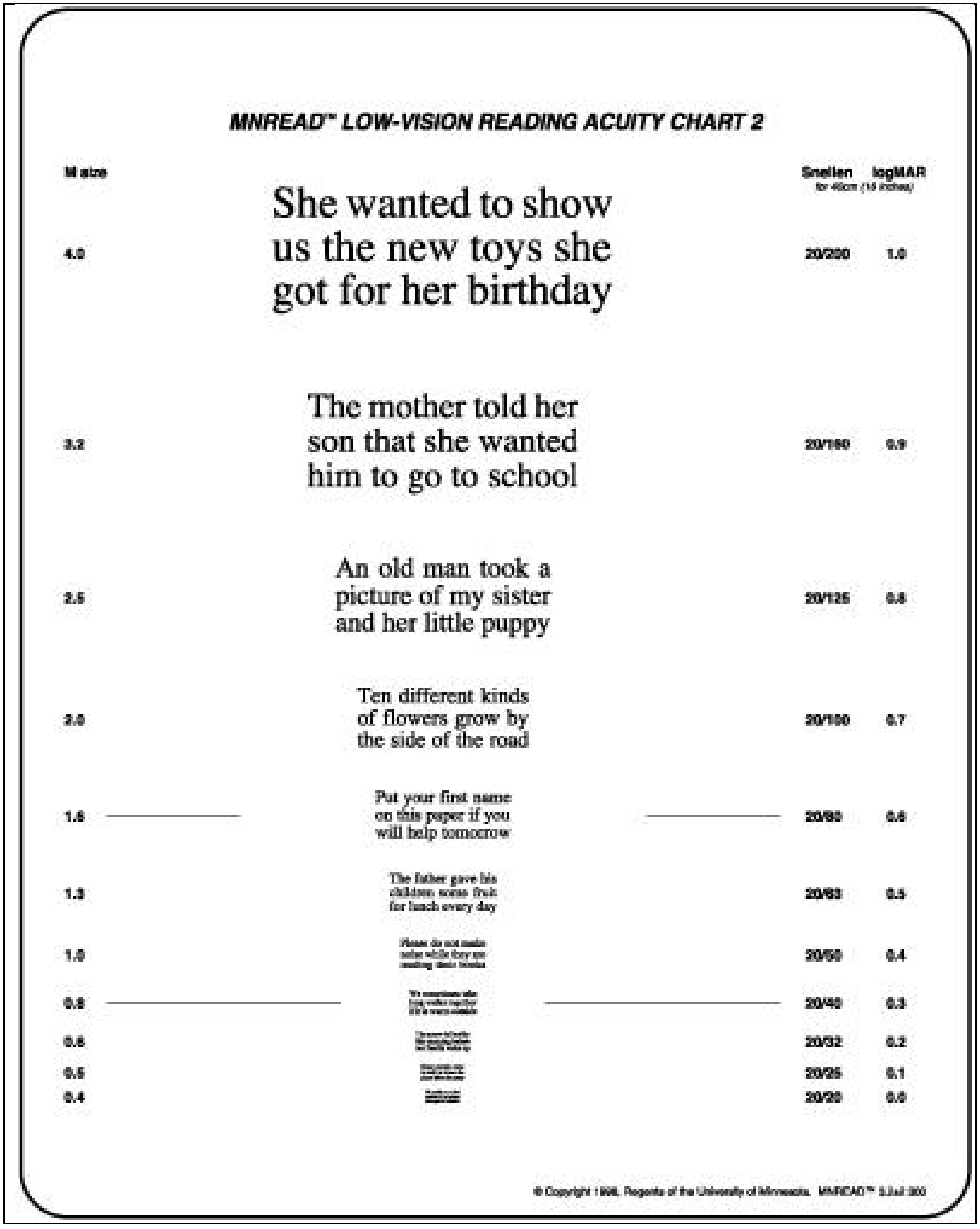
III. 20-50% (grade 2)

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
logMAR
for 40cm (16 inches)
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
20/50
0.4
0.8
20/40
0.3
0.6
20/32
0.2
0.5
20/25
0.1
0.4
20/20
0.0
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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

- 1 - *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

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

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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

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

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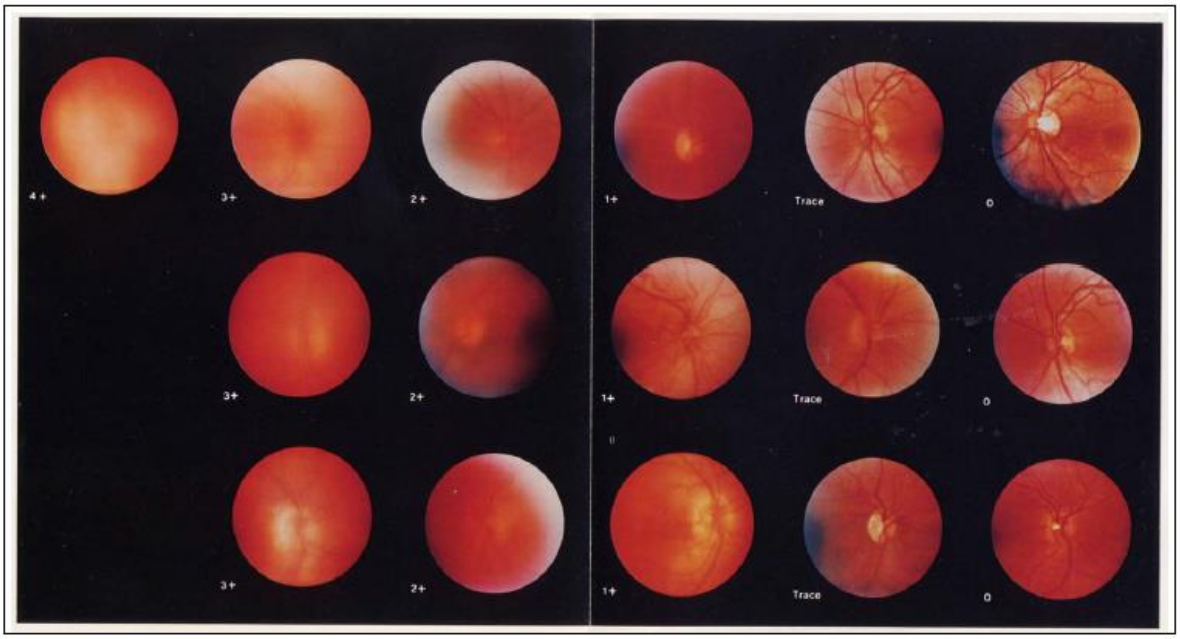
SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

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.