CONFIDENTIAL

FOCUS: AN OPEN LABEL FIRST IN HUMAN PHASE I/II MULTICENTRE STUDY TO EVALUATE THE SAFETY, DOSE RESPONSE AND EFFICACY OF GT005 ADMINISTERED AS A SINGLE SUBRETINAL INJECTION IN SUBJECTS WITH MACULAR ATROPHY DUE TO AGE-RELATED MACULAR DEGENERATION

PROTOCOL

Version:	9.0 (Global Amendment)
Version date:	15 Dec 2022
Superseded versions:	Version 8.0 (16 Feb 2022)
Sponsor:	Gyroscope Therapeutics
Product:	GT005
Study Number(s):	GT005-01/ NCT03846193
	EudraCT number: 2017-003712-39

Gyroscope Therapeutics Limited,
Rolling Stock Yard,
188 York Way,
London,
N7 9AS
United Kingdom

PROTOCOL SIGNATURES

Investigator Agreement and Signature:

I, the undersigned, have read and understood the GT005-01 (FOCUS) 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 Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and the laws and regulations of the country in which the study is being conducted.

Name:	
Title:	
Institution:	
Signature:	
Date:	

Sponsor's representative signature:

Name:	[redacted]
Title:	[redacted], Gyroscope
Signature:	DocuSigned by: [redacted]
Date:	15-Dec-2022

AMENDMENT HISTORY

Protocol Version	Change	Justification
V1, 04 DEC 2017	Initial	N/A
V1.1, 17 JAN 2018	Alteration of Inclusion criteria Pregnancy test requirements Clarification of CFI assay Stopping rules amended CFP requirements amended.	This amendment was created to address feedback from the MHRA.
V2.0, 18 SEP 2018	This protocol amendment includes: New preclinical safety information has been provided Cohort 2 dose changed Inclusion criteria added for microperimetry sub—study Revised details of pharmacovigilance services.	Emerging safety information.
V3.0, 02 MAY 2019	This protocol amendment includes: Revision of entry criteria to: • include all eligible atrophic AMD patients: those with a rare variant resulting in CFI haploinsufficiency as well as those without a CFI variant. The requirement for low serum CFI has also been removed • Clarify microperimetry requirement. At sites with a MAIA MP, all subjects will be assessed with a MP if feasible as assessed by the Investigator	GT005 has the potential to downregulate complement activation in all atrophic AMD, and there is no expectation that there would be differences in safety or tolerability in a broad atrophic AMD population; the two subpopulations will be analysed in the clinical endpoint analyses. As there are a limited number of subjects to evaluate the functional outcome of retinal sensitivity, this revision allows for inclusion of all subjects who may reasonably complete the assessment.
	Addition of a blood plasma sample collection at Dosing (Visit 2), Week 5 (Visit 4), Week 36 (Visit 7) or at Early Termination.	[redacted]
	Addition of microperimetry assessment at Week 12 (Visit 5) and at the Early Termination Visit.	Due to the small sample size in the study, these additional assessments give opportunity to collect more microperimetry data.

Protocol Version	Change	Justification
	Amending the secondary endpoints to: Remove: • Change from baseline in retinal/drusen volume Include: • Anatomical measures of retinal microstructures via SD-OCT [redacted]	Drusen volume cannot currently be calculated via the Heidelberg Spectralis. Inadvertently missed. Administrative adjustment to bring in line with the protocol.
	Efficacy assessments: Removing the requirement to assess GA area size via CFP.	CFP does not provide an accurate assessment of GA area size. Non-stereo images are sufficient to complete appropriate assessments.
	Correction of inconsistencies/inaccuracies.	
V4.0, 03 SEP 2019	This protocol amendment includes: • additional preclinical data supporting dose escalation to Cohort 3 • an additional dose level (Cohort 3) and a dose expansion cohort (Cohort 4) [redacted] • additional follow-up visits up to 4 years post-treatment	Preclinical data update. Revised study design allows a more comprehensive evaluation of safety, dose response and efficacy of GT005 in subjects with GA due to AMD. [redacted] The addition of a total follow-up period of 4 years post-treatment.
[redacted]	[redacted]	[redacted]

Protocol Version	Change	Justification
V5.0, 27 JAN 2020	This protocol amendment includes: • The addition of Cohorts 5 and 6 where the delivery of GT005 will be via the Orbit SDS device. • Both eyes are required to be eligible for subjects considered for Cohorts 4 to 6. The treated eye will be randomised for Cohorts 4 to 6. • Inclusion of a baseline serum CFI sample • Correction of inconsistencies/inaccuracies	The addition of Cohorts 5 and 6 (Part 3) is designed to evaluate GT005 delivered with the Orbit SDS device. In cohorts 4 to 6, both eyes must be eligible to be enrolled into the study. The treatment eye will be determined by a randomization step to remove potential selection bias and provide a more robust assessment of GT005 therapy when compared to the untreated contralateral eye. Inclusion of a separate serum sample at baseline to determine serum CFI levels which will be analyzed at the central laboratory (Eurofins).
V6.0/US, 12 MAY 2020 V6.0/UK, 13 MAY 2020	Schedule of Assessments.	Screening period extended, incorporated 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 only related SAEs from time of consent, all AEs from time of randomization.
	Inclusion/Exclusion Criterion.	Inclusion/exclusion criterion have been aligned with the Phase 2 studies in order to ensure more consistent study populations.
	Clarification regarding performing and obtaining genotyping results prior to commencement of screening assessments.	Given the low prevalence of CFI mutations and desire to minimize patient study activities, genotyping and serum CFI results will be received to confirm eligibility prior to other screening activities commencing.
	[redacted]	[redacted]
	Additional Week 8 Visit added.	To support additional safety monitoring, [redacted]

Protocol Version	Change	Justification
	[redacted]	[redacted]
	[redacted]	[redacted]
	Removed requirement to remain in medical facility overnight following surgery.	Emerging safety profile from the completed dose escalation in Part 1 of the study does not support need for overnight stay in a medical facility.
	Risk Section updated.	Updated risks to include those associated with topical steroid use. Added worsening of vision as a risk.
	[redacted]	[redacted]
	Added (serious) adverse device effect language, device deficiency definitions and reporting requirements.	Inclusion of Orbit SDS medical device for Cohort 5 and 6 surgeries.
	Updated guidance on GT005 destruction.	Provide more detailed instruction and clarity.
	Throughout the document.	Inconsistencies removed and language clarified. As these are minor revisions, they have not been summarised.
V6.1/UK, 17 NOV 2020	Reference to the Orbit SDS medical device and Cohort 5-6 removed throughout protocol.	Cohort 5 and 6 which includes delivery using the Orbit SDS device will not be conducted in the UK at this time.
	Remove reference to US region in protocol.	Protocol amendment specific to UK.
	Extension of the duration of subject participation in study from 4 to 5 years.	Subject participation duration has been extended to 5 years to better characterise long-term outcomes following GT005 treatment.
	Inclusion/Exclusion Criterion.	Inclusion criterion 4 has been updated to ensure the subjects have GA lesion residing completely within the FAF fundus image for both eyes. New exclusion criterion 4 has been added to provide clarification on timing of cataract surgery prior to screening. Exclusion criterion 12 updated to clarify requirements for medical history of malignancies.

Protocol Version	Change	Justification
	[redacted]	[redacted]
	Removal of randomisation step for Cohort 4.	When AMD occurs bilaterally, the disease may progress within patients' affected eyes at different rates. Central vision can be impacted non-uniformly across both eyes of the same patient, therefore resulting in a 'better seeing', or 'preferred' eye. Randomization of treatment eye was introduced in protocol v5.0 to minimize potential selection bias. However, on further review and feedback from study investigator(s), it is deemed more appropriate that the eye with the worse vision is selected by default, rather than using a randomisation method that may give rise to the better seeing eye being selected for surgery, particularly for an early phase clinical study with a less characterised safety profile. Randomisation of the patient's eye within Cohort 4 has therefore been removed.
	[redacted]	[redacted]
	Clarification of OCT modalities.	The differing OCT modalities have been clarified: 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, i.e. [redacted] any other safety-related changes.
	Include additional timepoints for collecting colour fundus photos and OCT imaging post-treatment.	Timepoints added to better characterise any anatomical or safety-related ocular changes post GT005 treatment.

Protocol Version	Change	Justification
	Screening and eligibility requirements for subjects.	To prevent repeating screening visits and all assessments more than once, data from subjects screened in another Gyroscope sponsored study, conducted at the same Investigative site as the FOCUS study, may be used to fulfil the screening and eligibility requirements for this study if they were performed within the study screening period.
	[redacted]	[redacted]
	AE Reporting language.	Safety reporting requirements updated to collect all AEs from date of consent.
	Throughout the protocol.	Administrative inconsistences removed and language clarified. As these are minor revisions, they have not been summarised.
V7.0/US, 01 DEC 2020	Addition of a dose-expansion Cohort 7. Increase in number of total subjects enrolled in study from 45 to 65.	Revised study design allows a more comprehensive evaluation of safety, dose response and efficacy of GT005, when administered using Orbit SDS device in subjects with GA due to AMD.
	Increase in overall study enrolment by 3.5 months.	To accommodate the enrolment of an additional to subjects in Cohort 7.

Protocol Version	Change	Justification
	Removal of randomization step for Cohort 4-6.	When AMD occurs bilaterally, the disease may progress within patients' affected eyes at different rates. Central vision can be impacted non-uniformly across both eyes of the same patient, therefore resulting in a 'better seeing', or 'preferred' eye. Randomization of treatment eye was introduced in protocol v5.0 to minimize potential selection bias. However, on further review and feedback from study investigator(s), it is deemed more appropriate that the eye with the worse vision is selected by default, rather than using a randomization method. A randomization method may give rise to the better seeing eye being selected for surgery, particularly for an early phase clinical study with a less characterised safety profile. Randomization of the subjects' eye within Cohort 4-6 has therefore been removed.
	Addition of OCT-A and FA.	OCT-A imaging added, if required, to identify potential CNV conversion during the study. FA included as an assessment to verify subjects do not have CNV at baseline or conversion to CNV during the study.
	Removal of reference to PRL identification prior to surgery.	Requirements surrounding PRL identification are described in the surgical manual.
	Extension of the duration of subject participation in study from 4 to 5 years.	Subject participation duration has been extended to 5 years to better characterize long-term outcomes following GT005 treatment.

Protocol Version	Change	Justification
	Inclusion/Exclusion Criterion (Cohort 4 to 7 only).	Inclusion criterion 4 has been updated to ensure the subjects have GA lesion residing completely within the FAF fundus image for both eyes. Inclusion criterion 5 broadened to BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent), to allow inclusion of subjects with worse-seeing vision who may benefit from GT005 treatment. New exclusion criterion 4 has been added to provide clarification on timing of cataract surgery prior to screening. Exclusion criterion 12 updated to clarify requirements for medical history of malignancies.
	[redacted]	[redacted]
	Amending the secondary endpoints to include: • To evaluate the performance of the Orbit SDS • To evaluate the safety of the Orbit SDS	Device-related endpoints added to more robustly characterize the performance and safety of the Orbit SDS.
	[redacted]	[redacted]
	Clarification of OCT modalities.	The differing OCT modalities have been clarified: 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, i.e., [redacted] any other safety-related changes.
	Include additional timepoints for collecting colour fundus photos and OCT imaging post-treatment.	Timepoints added to better characterize any anatomical or safety-related ocular changes post GT005 treatment.

Protocol Version	Change	Justification
	Screening and eligibility requirements for subjects.	To prevent repeating screening visits and all assessments more than once, data from subjects screened in another Gyroscope sponsored study, conducted at the same Investigative site as the FOCUS study, may be used to fulfil the screening and eligibility requirements for this study if they were performed within the study screening period.
	[redacted]	[redacted]
	AE Reporting language.	Safety reporting requirements updated to collect all AEs from date of consent.
	Throughout the protocol.	Administrative inconsistencies removed and language clarified. As these are minor revisions, they have not been summarised.
V7.1 (US), 30 MAR 2021	Clarify the window for conduct of the pre-operative study assessments.	Administrative inconsistencies between different protocol sections corrected and language clarified.
	Removal of the requirement for the blood pressure assessment to be conducted on the same arm throughout the study.	The blood pressure assessment may be conducted on either arm as there is no scientific requirement, under the context of this study, for blood pressure be collected on the same arm throughout the study.
	Removal of the requirement for OCT-A certification.	OCT-A certification requirements will be defined in the FOCUS Imaging Manual instead of the protocol.
	Removal of specified requirements for the Microperimetry assessment.	Microperimetry instructions will be provided in the imaging manual.
	In line with the clinical standard of care, CNV assessment may be performed in a step-wise manner with an initial evaluation made on the OCT and/or OCT-A images by the Central Reading Centre. In the event, that the OCT/OCT-A images are inconclusive to rule out the presence of CNV the subject will be required to undergo an additional assessment via FA.	Added clarification to the CNV assessment process to ensure alignment with clinical standard of care.

Protocol Version	Change	Justification
V8.0 (Global), 16 FEB 2022 Changes from V7.1 (US), 30 MAR 2021 and/or V6.1 (UK), 17 NOV 2020	US- and UK-specific protocols combined into a single global protocol. Unless specified, the changes detailed below apply to the amendment of both protocols.	To have a single global protocol.
	Clarification of the study design for the different treatment Cohorts between US and UK.	Provided clarity on the use of the Orbit SDS device in the US only for GT005 delivery for cohorts 5-7, as 510(k) cleared in the US.
	Specifically for the amendment of the UK protocol v6.1: The Orbit SDS and suprachoroidal cannulation are described, Cohorts 5-7 are included, and the study details for these cohorts are included. These changes are applied throughout the protocol (Synopsis, Section 1, Section 3, Section 6).	The US- and UK-specific protocols have been combined into a single global protocol. The Orbit SDS device will only be used in the US in cohorts 5-7 and was not included in the UK protocol v6.1.
	Specifically for the amendment of the UK protocol v6.1: update to the number of subjects to include the US-specific cohorts.	Update to number of subjects since Cohorts 5-7 only recruit subjects in the US and were not included in the UK protocol v6.1.
	Increase in number of study sites after combining US- and UK-specific protocols.	Specifically for the amendment of the UK protocol v6.1: The number of study sites increased to accommodate additional cohorts in the study from 10 sites, in up to 20 sites. Specifically for the amendment of the US protocol v7.1: The number of study sites increased to accommodate additional subjects in the study from 12 sites, in up to 20 sites.
	Study duration clarified, excluding, the recruitment duration.	Clarified the total study length post-treatment follow-up period is 5 years only and removed additional text relating to study recruitment.
	Provided further details of the screening assessments that should be repeated if the screening period is extended past the original 8-week screening period (8-12 weeks).	Provided clarification that if the screening period is extended to 8-12 weeks, the site staff need to repeat only the standard ophthalmic exam, haematology/biochemistry and visual acuity (BCVA and LLVA).

Protocol Version	Change	Justification
	Extension of the 8-week screening period up to 16 weeks in the event of GT005 deferral during surgery.	Clarified that in the event GT005 dosing was deferred during surgery, the time from screening may be extended up to 16-weeks Clarified that if the time from screening is extended past 12 weeks, in case of GT005 deferral, FAFs should be repeated in addition to the standard ophthalmic exam, haematology/biochemistry and BCVA/LLVA.
	Update to AE monitoring to allow for additional assessment.	Clarified that additional imaging or functional assessments may be conducted, as needed, to allow for safety assessment.
	[redacted]	[redacted]

Protocol Version	Change	Justification
	Consolidation and expansion of the objectives and evaluation criteria.	To include the objectives and evaluation criteria from both the US- and UK-specific protocols, and to further define the objectives and evaluation criteria.
	Reduced the number of primary objective evaluation criteria.	Updated to report the main primary objective/evaluation criteria assessed and clarified that the endpoint will be evaluated over 48 weeks.
	Update to the evaluation criteria for the secondary objective to evaluate the effect of GT005 on anatomical and functional visual outcomes.	Moved criteria on BCVA from the primary evaluation criteria to be reported as a secondary objective in the study. Added that the endpoints will be evaluated over 48 weeks.
	Update to secondary objectives for the Orbit SDS cohort in the US only.	Updated to include the specific endpoint and not the performance target. [redacted]
	[redacted]	[redacted]
	Inclusion/Exclusion Criteria.	To broaden and provide further clarity on the study eligibility criteria: Inclusion criterion 2 has been revised to include a broader population of patients with GA (unilateral or bilateral), with a requirement of AMD in the contralateral eye (except if the subject is monocular), but no requirement of GA in the fellow eye. Inclusion criterion 3 has been revised to allow GA lesion total size in the study eye ≥1.25mm2 with no upper limit in Cohort 7 only.

Protocol Version	Change	Justification
		Inclusion criterion 3 and criterion 4 have been revised to remove the requirement related to the GA lesion in the fellow eye in Cohorts 4 to 7. Inclusion criterion 5 has been revised to remove the BCVA requirement for the fellow eye in Cohorts 4 to 7. Exclusion criterion 1 has been revised to allow inclusion of subjects with CNV in the fellow eye (given specific criteria). Exclusion criteria 2, 3, 5, 6, and 7 have been revised to apply criteria to the study eye only, to broaden inclusion of subjects into the study.
	Specifically for the amendment of the UK protocol v6.1: Inclusion/Exclusion Criteria.	Inclusion criterion 5 broadened to BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent) for Cohorts 4 to 7, to allow inclusion of subjects with worse-seeing vision who may benefit from GT005 treatment. This inclusion criterion was previously broadened in the US protocol v7.1, but not the UK protocol v6.1. Exclusion criterion 14 added. This criterion applies to the US-specific cohorts, so was not included in the UK protocol v6.1.
	Options to perform the visual acuity check pre-surgery.	Provided clarification on the possibility to use ETDRS (not only Snellen) for pre-surgery visual acuity check.
	Specifically for the amendment of the UK protocol v6.1: OCT-A imaging added, if required, to identify potential CNV conversion during the study. OCT-A methodology included.	The US- and UK-specific protocols have been combined into a single global protocol. This change was previously made in the US protocol v7.1, but not in the UK protocol v6.1.

Protocol Version	Change	Justification
	Specifically for the amendment of the UK protocol v6.1: Removal of reference to PRL identification prior to surgery (requirements surrounding PRL identification are described in the surgical manual).	The US- and UK-specific protocols have been combined into a single global protocol. This change was previously made in the US protocol v7.1, but not in the UK protocol v6.1.
	Removal of reference to a “central” surgical site.	Clarification of terminology that subjects will undergo subretinal surgery at the study site.
	Removal of text describing procedures for destruction of GT005	This information will be included within the pharmacy manual
	[redacted]	[redacted]
	[redacted]	[redacted]
	Risk/benefit analysis update to include that GT005 is in early clinical development.	Clarified that the potential risks of GT005 have also been evaluated in preliminary clinical data (in humans).
	Update to reason for screen failure.	Clarified that eligible subjects who do not receive treatment, can be replaced and classed as screen failures.
	Update of the list of options for action taken regarding study drug in the adverse event reporting section.	To more accurately document this information.
	Update of the device malfunction definition.	For clarification.
	Specifically for the amendment of the UK protocol v6.1: inclusion of definition and reporting of device specific AEs, and a section on device malfunctions.	The US- and UK-specific protocols have been combined into a single global protocol. There was no device-related information in the UK protocol v6.1.
	Update to clarify the statistical methods and analysis. Update to define the Safety Set and Full Analysis Set.	To more fully describe the planned statistical analyses by dose, route of administration and for both eyes. Clarified that the Safety Set (SS) will be used for analysis of safety and laboratory data. The Full Analysis Set will include all subjects in SS who have baseline and at least one post-baseline value of GA area size via FAF in the study eye.

Protocol Version	Change	Justification
	A more detailed description of the role of the IRB/REC and Competent Authority is included.	Alignment of the US- and UK-specific protocols to combine into a single global protocol.
	DSMB meeting schedule update.	Clarification that additional DSMB meetings can be held as needed or at the request of the DSMB members.
	GT005 will be labelled in accordance with specific local requirements.	The US- and UK-specific protocols have been combined into a single global protocol, therefore, clarified that labelling of GT005 with occur in line local requirements.
	Orbit SDS (US only) regulatory guidance on labelling.	Clarification labelling will be in accordance with FDA regulations for marketed products only.
	Schedule of events updated in line with changes in the protocol.	For consistency.
	Genetic testing and confidentiality of trial documents and subject records updated.	Updated to include that the distribution of genetic data is carefully controlled.
	Administrative changes throughout the protocol.	Administrative inconsistencies removed, and language clarified in the study design figure and throughout the protocol. As these are minor revisions, they have not been summarised. For consistency with other clinical protocols, updated the term macular atrophy to geographic atrophy, secondary to AMD. For consistency, low dose, [redacted] have been defined, where appropriate. Update to change in Sponsor address. For consistency, updated the Transvitreal Surgical Procedure Manual and Orbit SDS Surgical Procedure Manual to relevant Surgical Manual. Alignment of the protocol signature page to global protocols.

Protocol Version	Change	Justification
V9.0 (Global), 15 Dec 2022 Changes from V8.0 (Global)	[redacted]	[redacted]
	[redacted]	[redacted]
	Updated the Synopsis and Section 2 Study Objectives to: • Evaluate long-term safety of GT005 at 3 doses (in up to 240 Weeks) • Clarify secondary and [redacted] endpoints to be reported through Week 240	• Included a new secondary objective and report the long-term safety of GT005 until the end of study • Clarified the analysis timepoints for secondary and [redacted] endpoints to be reported until the end of study
	• Updated recent information under Section 1.6.1.1, 'Risks associated with GT005'	• This section has been aligned with the current version of the Investigator's Brochure (IB)
	• Clarification to Section 11.3.2 Statistical Analysis, Efficacy that Interim analyses may be considered	• To help inform internal development decision points for GT005. Details will be pre-specified in the SAP prior to conducting the analysis
	• Added Section 8.2.4, footnote 15 (Table 2) and footnote 9 (Table 3) in the Schedule of Assessments to include the submission of historical FAF and OCT images by the sites	• To obtain individual historical information on natural GA disease progression prior to enrolment and treatment in the study, for potential data sub analyses
	• Updated Section 7 Study Plan and Footnote 1 (Table 1, Table 2, Table 3) in the Schedule of Assessments to include definition of the Surgical Site	• To optimise operational management of the study and clarify where the study assessments can be conducted, the definition of surgical site has been included

Protocol Version	Change	Justification
	Updated Section 7.8, Section 7.10, Section 7.13, Section 7.14, Section 7.15, [redacted]	• For consistency with other clinical protocols and to prevent sampling error
	• Update to the Schedule of Assessments, OCT-A and FA. In Table 2, Footnote 8 and Table 3, Footnote 4 were added to follow-up visits, to clarify that OCT-A and/or FA may be performed if clinically indicated during follow-up	• The Schedule of Assessments has been aligned with the main body of the protocol under Section 7 for consistency
	• Added Section 7.18.2 for Post Week 48 Early Termination assessments and updated the Early Termination Visit Scheduled Assessments to overlap with the Unscheduled Visit Assessments for Table 3	• To clarify Early Termination procedures, post week 48 during the long term follow-up study visits
	• Updated Section 8.2.3, [redacted] footnote 14 (Table 2) and footnote 5 (Table 3) to clarify that simultaneous binocular testing is not required in this study	• To provide guidance on the assessments required for [redacted]
	• Updated Section 6.9 Drug and Surgical Device Accountability to include that devices should be returned upon the end of study enrolment instead of at the end of study	• Further clarity on return of surgical devices has been provided
	• Removal of Steering Committee from the Synopsis and Section 24	• Removed reference to this study-specific steering committee that is no longer in place, and has been superseded by other sponsor scientific and clinical advisory boards

Protocol Version	Change	Justification
	• Administrative Changes	• Update to Sponsor Name on Title page since Gyroscope was acquired by Novartis in February 2022 • Clarification to Synopsis and Section 3 Study Design, Figure 1 titled "Overview of the Study Design (Parts 3 and 4 are US Only)" for Cohort 7 to state n=up to 20, as per the main body of the protocol • 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 • Update to footer enumeration on Table 1, Table 2, and Table 3 as re-enumeration was required as a result of updating SOA footers to incorporate the changes identified in this table • Updated term Statistical Set to Statistical Analysis Set and corresponding abbreviation SS to SAF

Abbreviations: AEs=adverse events; AESI=adverse events of special interest; AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CFI=complement factor I; CFP=colour fundus photography; CNV=choroidal neovascularisation; COVID-19=Coronavirus Disease 2019; DSMB=data safety monitoring Board; FA=Fluorescein angiography; FAF=fundus autofluorescence; GA=geographic atrophy (also known as macular atrophy); FAS=full analysis set; MAIA=macular integrity assessment; MHRA=Medicines and Healthcare products Regulatory Agency; MP=microperimeter; N/A=not applicable; OCT=Optical coherence tomography; OCT-A=optical coherence tomography angiography; PRL=preferred retinal locus; SAE=serious adverse event; SD-OCT=spectral domain optical coherence tomography; SDS=subretinal delivery system; SAF=safety analysis set; V=version; [redacted].

PROTOCOL SYNOPSIS

TITLE:

FOCUS: An open label first in human Phase I/II multicentre study to evaluate the safety, dose response and efficacy of GT005 administered as a single subretinal injection in subjects with macular atrophy due to age-related macular degeneration

PROTOCOL NO:

GT005-01

INVESTIGATOR STUDY SITES:

All subjects will undergo subretinal surgery at a surgical site. Subject recruitment and most follow-up visits will be conducted in up to 20 study sites (including the surgical sites).

STUDY PERIOD:

Total study length is estimated to be 5-years post-treatment follow-up period.

OBJECTIVES:

The overall objectives of the study are to evaluate the safety, the dose response and efficacy (anatomical and functional visual outcomes) of three doses of GT005 in subjects with geographic atrophy (GA, also known as macular atrophy) due to age-related macular degeneration (AMD) when delivered subretinally via the transvitreal procedure or suprachoroidal cannulation.

INVESTIGATIONAL MEDICINAL PRODUCT:

Name and Description of GT005:

A recombinant adeno-associated virus vector (AAV) derived from wild-type AAV serotype 2 (AAV2). The expression cassette contains deoxyribonucleic acid encoding for human complement factor I (hCFI).

METHODOLOGY:

This is an open label first in human Phase I/II multicentre study to evaluate the safety, dose response and efficacy of GT005 in subjects with GA due to AMD. The study will be conducted in four parts; Part 1 (Cohorts 1 to 3): dose-escalation, Part 2 (Cohort 4): dose-expansion, Part 3 (Cohorts 5 to 6): dose-escalation with the Orbit Subretinal Delivery System (SDS), and Part 4 (Cohort 7): dose-expansion with the Orbit SDS.

Parts 1 and 2 (Cohorts 1 to 4) will deliver GT005 via the standard transvitreal procedure and Parts 3 and 4 (Cohorts 5 to 7) will deliver GT005 via the Orbit SDS.

The Orbit SDS is a 510(k) cleared device in the United States (US) whereby Parts 3 and 4 (Cohorts 5 to 7) will only be used at US sites.

Part 1 (Cohorts 1 to 3; dose-escalation) will test three dose cohorts (low dose, [redacted]; [redacted] vector genomes [vg]) of up to five subjects per cohort. Sentinel dosing will be applied whereby there will be a minimum of 14 days separation between dosing of the first and second subject of each dose cohort, to assess any acute reactions to surgery and the short-term tolerability to GT005 prior to dosing the remaining subjects in each dose cohort. Dose-escalation will be evaluated by a Data Safety Monitoring Board (DSMB) and will be assessed based on the Week 5 safety data for the first three subjects dosed in each of Cohorts 1 and

2. The DSMB will review the Week 5 safety data for the first three subjects dosed in Cohort 3 prior to dosing in further cohorts.

Subjects will receive a single subretinal injection of GT005 at one of three dose levels:

- [redacted] AAV2 vg in 100 microlitres
- [redacted] AAV2 vg in 100 microlitres
- [redacted] AAV2 vg in 100 microlitres

Part 2 (Cohort 4; dose-expansion) will enrol up to 20 subjects in Cohort 4 with GT005 delivered via the transvitreal procedure to further characterise the safety, dose response, and efficacy of GT005. On completion of dose-escalation, dose levels determined to be safe and tolerable by the DSMB in Part 1 (Cohorts 1 to 3), may be assessed in Cohort 4. The exact number of subjects that will be enrolled in Cohort 4 will be determined by the Sponsor based on the emerging safety, pharmacodynamic and clinical outcomes data.

Part 3 (Cohorts 5 to 6; dose-escalation and evaluation of two doses of GT005 delivered with the Orbit SDS; subretinal delivery via a suprachoroidal cannulation) will enrol three to five subjects at the mid dose ([redacted] vg; Cohort 5) and three to five subjects at the high dose ([redacted] vg; Cohort 6), to evaluate the safety of GT005 treatment when delivered via the Orbit SDS. Part 3 (Cohorts 5 to 6) is independent of, and may be conducted in parallel to, Part 2 (Cohort 4). Dose-escalation will be evaluated by the DSMB and will be assessed based on the Week 5 safety data for the first three subjects dosed in Cohort 5.

Part 4 (Cohort 7) dose-expansion of GT005 delivered with the Orbit SDS; subretinal delivery via a suprachoroidal cannulation) will enrol up to 20 subjects in Cohort 7 to further characterise the safety, dose response, and efficacy of GT005 treatment when delivered via the Orbit SDS. On completion of dose-escalation, dose levels determined to be safe and tolerable by the DSMB in Part 1 (Cohorts 1 to 3) may be assessed in Cohort 7. The exact number of subjects that will be enrolled in Cohort 7 will be determined by the Sponsor based on the emerging safety, pharmacodynamic and clinical outcomes data.

The study treatment consists of an AAV2 expressing hCFI. The treatment is administered as a single subretinal injection into one eye – “the study eye”. Both eyes will be assessed at the screening visit. If both eyes meet the eligibility criteria the study eye will be the worse seeing eye or the eye with the largest GA size for eyes with equivalent visual acuity unless the patient (in consultation with the surgeon) expresses an alternative preference.

The study will, for the individual subjects, consist of up to 13 visits over a 5-year period. All subjects will be assessed for the occurrence of adverse events (AEs) at each visit and will undergo functional visual and retinal imaging/anatomical assessments and biological sampling as per the schedule of assessments.

Objectives	Evaluation Criteria
Primary	
• To evaluate the safety of GT005 at 3 doses	• Incidence of ocular and non-ocular treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs) over 48 weeks
Secondary	
• To evaluate long-term safety of GT005 at 3 doses	• Incidence of ocular and non-ocular treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs) up to 240 weeks
• To evaluate the effect of GT005 on anatomical and functional visual outcomes	• Best corrected visual acuity (BCVA) and low luminance visual acuity (LLVA) score via the early treatment diabetic retinopathy study (ETDRS) chart up to 240 weeks • Macular sensitivity as assessed by Mesopic Microperimetry up to 240 weeks • Change in GA area size as assessed by fundus autofluorescence (FAF) up to 240 weeks
• To evaluate the performance of the Orbit SDS (US only)	• Rate of successful delivery of balanced salt solution (BSS) or BSS PLUS to the subretinal space • Rate of successful delivery of GT005 to the subretinal space
• To evaluate the safety of the Orbit SDS (US only)	• Incidence of device-related AEs and SAEs
[redacted]	
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted]

	• [redacted]

Following consent, subjects will undergo several ophthalmic and clinical assessments to determine eligibility for inclusion in the study. Once eligibility is confirmed by the Sponsor the subject will be enrolled. The subject will be scheduled for surgery [redacted]

Subretinal surgery and administration of GT005 will take place at a surgical site. [redacted]

During surgery, [redacted] The surgery will be performed under local anaesthesia. Other anaesthetic options will be considered by the surgeon as appropriate for the subject. Then subjects will receive GT005 at one of the three doses ([redacted]) as a single administration in the form of a subretinal injection of 100 microlitres. After surgery, subjects will remain in the clinic for up to 24 hours following the surgery to assess any acute issues resulting from the surgery. [redacted]

Subjects will undergo follow-up visits at Week 1, 5 and 8 post-dosing, every three months post-dosing (at Weeks 12, 24, 36, and 48) for the first year, and at Weeks 72 (1.5 years), 96 (2 years), 144 (3 years), 192 (4 years), and 240 (5 years) post-dosing. At the Week 48 visit, subjects will be invited to consent to the additional follow-up (up to and including Week 240 visit). The Week 48 visit will be the time point used for the primary endpoint of the study. Week 240 (Year 5) will be the end of the study.

NUMBER OF SUBJECTS:

Approximately 65 subjects will be enrolled: up to five in each of Cohorts 1 to 3, up to 20 in Cohort 4, up to five in each of Cohorts 5 and 6, and up to 20 in Cohort 7.

Subjects who are screened but do not receive treatment, will be classed as screen failures and may be replaced. The 8-week screening period may be extended up to 12 weeks if agreed by the Sponsor Medical Monitor. If the screening period is extended past the original 8-week screening period (8–12 weeks), standard ophthalmic exam, haematology/biochemistry, and visual acuity (BCVA/LLVA) assessments should be repeated. In the event the GT005 administration is deferred during the surgical procedure (e.g., due to an AE occurring during surgery) the screening period may be extended up to 16 weeks if agreed by the Sponsor Medical Monitor. Additionally, if the screening period is extended past 12 weeks (12–16 weeks), in case of GT005 deferral, standard ophthalmic exam, haematology/biochemistry, visual acuity (BCVA/LLVA), and FAFs will be repeated.

In the event, that a subject withdraws from the study for any reason other than an AE or other safety concern or is lost to follow-up within 6 months (Week 24) post

dosing, the subject may be replaced. The reason for the subject's withdrawal from the study must be recorded.

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

1. Able and willing to give consent to study participation
2. 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)
3. Cohorts 1 to 6: GA lesion(s) total size in the study eye must be ≥1.25mm^2 and ≤17.5mm^2

   Cohort 7: GA lesion(s) total size in the study eye must be ≥1.25mm^2
4. GA lesion(s) in the study eye must reside completely within the FAF fundus image
5. Cohorts 1 to 3: BCVA of ≤50 letters (6/36 Snellen acuity equivalent or worse) using ETDRS charts in the study eye

   Cohorts 4 to 7: BCVA of ≥24 letters (6/95 and 20/320 Snellen acuity equivalent or better) using ETDRS charts in the study eye
6. Aged ≥55 years
7. Able to attend all study visits and complete the study procedures
8. Women of child-bearing potential need to have a negative urine pregnancy test within two weeks prior to receiving the drug. 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. Have evidence or history of choroidal neovascularisation (CNV) in the study eye. Subjects 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
2. Presence of moderate/severe non-proliferative diabetic retinopathy or worse in the study eye
3. Have history of vitrectomy, sub-macular surgery, or macular photocoagulation in the study eye
4. History of intraocular surgery in the study eye within 12 weeks prior to Screening (Visit 1). [redacted]
5. Have clinically significant cataract that may require surgery during the study period in the study eye

6. 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 is also excluded
7. Axial myopia of greater than -8 diopters in the study eye
8. Have received any investigational product for the treatment of GA within the past 6 months or 5 half-lives (whichever is longer), other than nutritional supplements such as the age-related eye disease study (AREDS) formula
9. Have received a gene or cell therapy at any time
10. Have a contraindication to the specified protocol corticosteroid regimen
11. Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant
12. 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
13. 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
14. Cohorts 5 to 7 only: presence of metallic objects or implanted stimulator devices in or near the head, including cochlear implants, deep brain stimulators, vagus nerve stimulators, and other implanted electrodes or stimulators

DOSE/ROUTE/REGIMEN:

The study drug is supplied to the surgical site as a vial of frozen sterile liquid.

GT005 is an aqueous suspension of recombinant AAV2 vector particles in [redacted] GT005 is administered at ambient temperature as a single subretinal injection into the macula of the study eye.

Surgical procedure

GT005 will be administered subretinally via the transvitreal procedure for Cohorts 1 to 4, an approach which is based on publicly available methodology. GT005 will be administered subretinally via a suprachoroidal cannulation with the Orbit SDS for Cohorts 5 to 7 (US sites only). All Cohorts will be treated by an appropriately qualified vitreoretinal surgeon in an operating room under local anaesthesia. Other anaesthetic options will be considered by the surgeon as appropriate for the subject. The total duration of the surgery is about 1 hour. The detailed procedure is described in the relevant Surgical Manuals.

In brief:

Cohorts 1 to 4

[redacted]

Cohorts 5 to 7 (US sites only)

[redacted]

DURATION OF TREATMENT AND FOLLOW-UP

Subjects will receive a single subretinal injection and will be followed for up to 240 weeks (5 years) post-dosing.

REFERENCE TREATMENT:

Only one eye will be treated in the study and the untreated fellow eye will be the comparator.

The eye with the worse visual acuity will be 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 patient (in consultation with the surgeon) expresses an alternative preference. The study eye will be confirmed by the vitreoretinal surgeon.

STATISTICAL METHODS: All the efficacy data (anatomical and functional visual outcomes), [redacted] and [redacted] data and safety data (including laboratory safety) collected will be amalgamated into a single database with datasets constructed according to these categories. Unless otherwise stated, data will be summarised in aggregate by dose and route of administration. Further detail will be described in the statistical analysis plan.

Analysis Set

Two analysis sets will be defined. The Safety Analysis Set (SAF) will include all subjects who have undergone surgery and received GT005. The SAF will be used for analysis of safety and laboratory data. The Full Analysis Set (FAS) will include all subjects in the SAF who have baseline and at least one post-baseline value of GA area size via FAF in the study eye. The FAS will be used for analysis of efficacy data.

Data Descriptions

Data will be summarised by the subject population (SS, FAS, and subsets as applicable), Cohort/dose group (Cohorts 1 to 7, dose group [redacted] vg, and overall subjects), eye (Treated [Study Eye]/Untreated [Fellow Eye] for ocular evaluations and tests), and assessment (Weeks 1 to 48, or early termination, where appropriate). The long-term follow-up data (Visits 9 to 13) will be reported separately.

Categorical variables will be summarised as the number and percentage of subjects, and frequencies of events (if appropriate). Continuous variables will be summarised as number of subjects, mean, median, standard deviation, minimum, and maximum statistics. Graphical displays appropriate to these types of data may be used to present any important findings.

Demographics and Baseline Characteristics

Medical history and measures at baseline including: demographics, medical/surgical history, concomitant medication, laboratory safety, urine pregnancy testing will be summarised descriptively by dose and route of administration. No formal comparisons of the Cohorts will be made. Assessments made at screening/baseline

and post-surgery will only be included in their respective safety and efficacy tables, together with any post-baseline assessments.

Efficacy Assessments

Efficacy assessments to evaluate the anatomical and functional visual outcomes involve: GA area size (via FAF), [redacted]. For continuous variables, the change from baseline will be derived and presented together with actual values over time (visit) by dose and route of administration, and by eye (Treated [Study Eye]/Untreated [Fellow Eye]). Categorical variables from any ocular evaluations will be presented by classification over time (visit) by dose and route of administration, and by eye (Treated [Study Eye]/Untreated [Fellow Eye]).

[redacted]

Safety Assessments

Safety evaluations are considered to be of key importance for this study and include: AEs, ophthalmic examinations, BCVA (ETDRS) score, vital signs, laboratory safety (biochemistry and haematology), and [redacted]

Adverse events will be summarised in two parts: systemic events and ocular events. For systemic events, data will be summarised by dose and route of administration. Ocular events will be summarised by dose and route of administration and by eye (Treated [Study Eye]/Untreated [Fellow Eye]).

All AEs (Overall, by seriousness, by severity, by relationship to GT005 or the procedure) recorded throughout the investigation will be reported following classification according to the Medical Dictionary for Regulatory Activities dictionary (for system organ class and preferred term).

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

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, dependent on data type.

Power and Sample Size

As this is a first in human exploratory Phase I/II study, no formal sample size has been calculated.

MONITORING COMMITTEES

Data Safety Monitoring Board (DSMB)

Composition

A DSMB will be formed to review all safety data at predetermined intervals during the study. Additional DSMB meetings may be held as needed or at the request of the DSMB members. The DSMB is an independent committee that includes at least three individuals who cumulatively have the clinical and medical expertise to monitor the safety of subjects in the clinical study and will include a minimum of

one clinician expert in the management of AMD and clinical immunology. The DSMB will be chaired by one of the clinical experts who will attend all meetings. No DSMB member will be an Investigator in this study.

Roles and Responsibilities of DSMB

The roles and responsibilities of the DSMB are defined in the DSMB Charter, which include, but are not limited to:

- Monitoring and reviewing all safety issues relative to the conduct of the study
- Ensuring the protection and safety of subjects participating in the study
- Recommending dose escalation in accordance with available safety data and study stopping rules
- Recommending a different BCVA threshold for entry into the study, as appropriate
- Providing recommendations to continue, modify the design, suspend or terminate the study depending upon emerging safety data
- Communicating other recommendations or concerns as appropriate

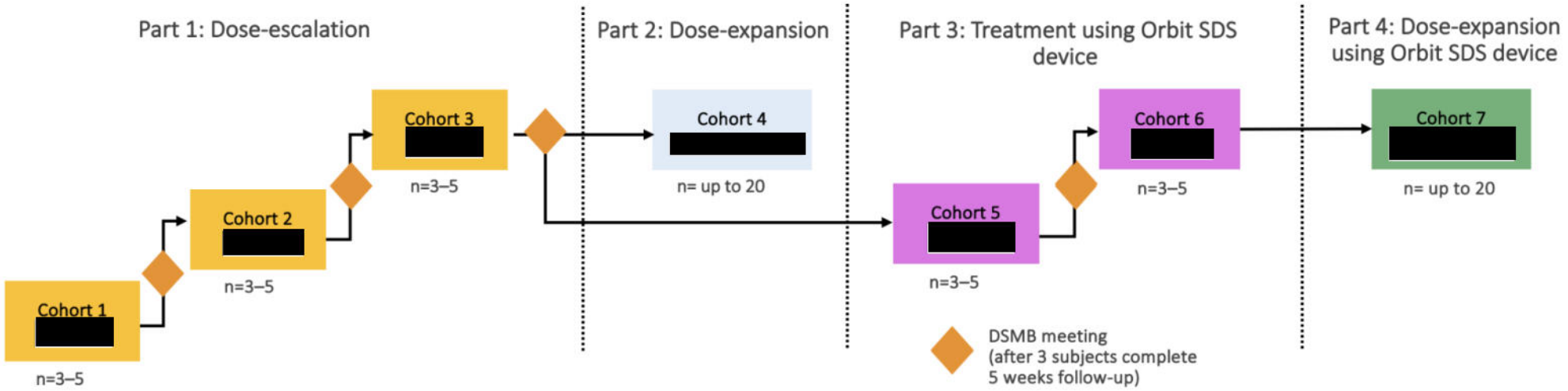
Dose Escalation

- The DSMB will meet after the third subject has been enrolled (recruitment and treatment will continue at the current dose – there will be no study hold) in Cohorts 1 to 3, and in Cohort 5
- If treatment has been tolerated and stopping rules have not been met, the DSMB will recommend to Gyroscope that enrolment of the next study Cohort can commence
- Screening of potential subjects will be allowed prior to the DSMB meeting and decision, but treatment must not be administered to subjects in the higher dose group until the outcome of the DSMB recommendation has been provided in writing to Gyroscope

Details regarding the DSMB mission and content of the DSMB data safety reviews will be specified in the DSMB charter.

STUDY DESIGN

Figure 1: Overview of the Study Design (Part 3 and 4 are US only)



Abbreviations: DSMB=data safety monitoring board; n=number of subjects; SDS=subretinal delivery system; vg=vector genomes.

SCHEDULE OF ASSESSMENTS

Table 1: Clinical Schedule (Screening to Week 48)

	Local Site[1]	Surgical Site						Surgical or Local Site			Local Trial Site[1]			
Assessment	Visit 1 Screening[2] Day -56 to -1 (-8 weeks)	Visit 2 Dosing			Tel call	Visit 3[4] Week 1 ±3 days	Tel call Week 2 ±3 days	Visit 4 Week 5 -7/+3 days	Visit 4.1 Week 8 ±7 days	Visit 5 Week 12 ±7 days	Visit 6 Week 24 ±7 days	Visit 7 Week 36 ±7 days	Visit 8 Week 48 ±7 days	Early Termination Visit
		Pre-surgery Day 1[3]	Surgery Day 1	Post-surgery Day 2										
Informed consent	X												X[5]	
Review of Inc/Exc criteria	X													
Demographics	X													
Medical/surgical history	X	X												
Concomitant medication	X	X		X		X		X	X	X	X	X	X	X
[redacted]														
Urine pregnancy test[6]	X	X[7]												
Vital signs	X	X		X		X		X		X	X	X	X	X
Biochemistry/Haematology	X					X		X		X	X	X	X	X
[redacted]														
Serum sample for CFI levels[8]	X													
[redacted]														
Sample for sequencing of complement genes[8]	X													
Surgery and dosing (GT005)			X											
Discharge from unit				X										
[redacted]														
Adverse events – AE/TEAE/TESAE[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Local Site[1]	Surgical Site						Surgical or Local Site			Local Trial Site[1]			
Assessment	Visit 1 Screening[2] Day -56 to -1 (-8 weeks)	Visit 2 Dosing			Tel call	Visit 3[4] Week 1 ±3 days	Tel call Week 2 ±3 days	Visit 4 Week 5 -7/+3 days	Visit 4.1 Week 8 ±7 days	Visit 5 Week 12 ±7 days	Visit 6 Week 24 ±7 days	Visit 7 Week 36 ±7 days	Visit 8 Week 48 ±7 days	Early Termination Visit
		Pre-surgery Day 1[3]	Surgery Day 1	Post-surgery Day 2										

Abbreviations: AAV2=adeno-associated virus vector serotype 2; AE=adverse event; BCVA=best corrected visual acuity; CFI=complement factor I; FAF=fundus autofluorescence; ICF=informed consent form; Inc/Exc=inclusion/exclusion; LLVA=low luminance visual acuity; TEAE=treatment-emergent adverse events; Tel=telephone; TESAE=Treatment-emergent serious adverse events.

1. Dependent upon location and Sponsor approvals, a Surgical Site may also act as a Local Site.
2. Screening assessments may be conducted over several days. The 8-week screening period may be extended up to 12 weeks if agreed by the Sponsor Medical Monitor. If the screening period is extended past the original 8 week screening period (8-12 weeks), standard ophthalmic exam, haematology/biochemistry, and visual acuity (BCVA/LLVA) assessments should be repeated. In the event the GT005 administration is deferred during the surgical procedure (e.g., due to an AE occurring during surgery) the screening period may be extended up to 16 weeks if agreed by the Sponsor Medical Monitor. Additionally, if the screening period is extended past 12 weeks (12–16 weeks), in case of GT005 deferral, standard ophthalmic exam, haematology/biochemistry, visual acuity (BCVA/LLVA), and FAFs will be repeated.
3. Pre-surgery assessments will include any local requirements of the surgical site. Pre-surgery assessments should be performed within 7 days prior to surgery.
4. Visit 3 will take place at the assigned surgical site, however this may be held at the local site if more practical.
5. Subjects will be consented using a separate ICF for the additional four years of long-term follow-up at this visit.
6. Only for women of childbearing potential.
7. Urine pregnancy test (for women of childbearing potential) if the one performed at screening is more than 14 days old.
8. Not required at Screening if already available through participation in a previous Gyroscope sponsored study.

[redacted]

14. 12 to 24 hours post dosing, prior to discharge.
15. All AEs should be captured from signing the informed consent form. Additional imaging or functional assessments may be conducted, as needed, to allow for safety assessment.

Table 2: Schedule of Visual Tests (Screening to Week 48)

Assessment	Local Site[1]	Surgical Site						Surgical or Local Site			Local Trial Site[1]			Early Termination Visit
	Visit 1 Screening[2] Day -56 to -1 (-8 weeks)	Visit 2 Dosing			Tel call	Visit 3[4] Week 1 ±3 days	Tel Call Week 2 ±3 days	Visit 4 Week 5 -7/+3 days	Visit 4.1 Week 8 ±7 days	Visit 5 Week 12 ±7 days	Visit 6 Weeks 24 ±7 days	Visit 7 Week 36 ±7 days	Visit 8 Week 48 ±7 days	
		Pre-surgery Day 1[3]	Surgery Day 1	Post-surgery Day 2										
Standard ophthalmic examination	X			X		X		X	X	X	X	X	X	X
Pre-surgery ocular safety check		X[5]												
Colour fundus photography	X									X	X	X	X	X
Fundus autofluorescence	X							X		X	X	X	X	X
OCT macula	X			X		X		X		X	X	X	X	X
[redacted]														
OCT-A[7]	X					X[8]								X[8]
Fluorescein angiography[7]	X					X[8]								X[8]
Microperimetry[9]	X	X[10]								X	X		X	X
Additional functional assessments (if required)[11]								X[11]						X[11]
Visual Acuity: BCVA and LLVA using ETDRS	X					X[12]		X[12]	X[12]	X	X	X	X	X
Visual acuity check		X[13]												
[redacted]														

[redacted]

Submission of historical FAFs and/or OCTs[15]	X

Abbreviations: BCVA=best corrected visual acuity; CNV=choroidal neovascularisation; ETDRS=early treatment diabetic retinopathy study chart; FA=fluorescein angiography; LLVA=low luminance visual acuity; MAIA=macular integrity assessment; MNRead=Minnesota low vision reading; OCT=optical coherence tomography; OCT-A=optical coherence tomography angiography; Tel=telephone; [redacted].

1. Dependent upon location and Sponsor approvals, a Surgical Site may also act as a Local Site
2. Screening assessments may be conducted over several days. The screening period may be extended up to a maximum of 12 weeks, if agreed by the Sponsor Medical Monitor. If the screening period is extended past the original 8-week screening period (8-12 weeks), standard ophthalmic exam, haematology/biochemistry, and visual acuity (BCVA/LLVA) assessments should be repeated. In the event the GT005 administration is deferred during the surgical procedure (e.g., due to an AE occurring during surgery) the screening period may be extended up to 16 weeks if agreed by the Sponsor Medical Monitor. Additionally, if the screening period is extended past 12 weeks (12–16 weeks), in case of GT005 deferral, standard ophthalmic exam, haematology/biochemistry, visual acuity (BCVA/LLVA), and FAFs will be repeated.
3. Pre-surgery assessments should be performed within 7 days prior to surgery.
4. Visit 3 will take place at the surgical site, however this may be held at the local site if more practical.
5. A pre-surgery ocular safety check will be performed to verify no new adverse events that could halt surgery.

[redacted]

7. Other imaging modalities may be performed to assess for CNV if OCT-A is not available. In the event that the OCT/OCT-A images are inconclusive to rule out the presence of CNV the subject will be required to undergo an additional assessment via FA. At the Investigator's discretion, FA may also be performed initially prior to the OCT/OCT-A results being available, but this is not mandatory.
8. OCT-A and/or fluorescein angiography may be performed during the study period if clinically indicated, for example, if a subject converts to wet AMD.
9. Microperimetry should be performed during scheduled visits at sites with a MAIA microperimeter: Microperimetry will be performed at either screening or prior to surgery (within the screening visit window) and may be performed over >1 day if needed. If in the view of the Investigator, the subject is not capable of performing the test, this will not be considered an exclusion to study participation. Microperimetry assessment instructions will be provided in the imaging manual.
10. If omitted at screening, assessments should be performed during the pre-surgery visit.

[redacted]

12. LLVA is not performed at Visits 3, 4 and 4.1.
13. A visual acuity check using ETDRS or 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. If Snellen result is >3 lines (BCVA equivalent to 15 letters) worse than the previous BCVA ETDRS score, then a BCVA with ETDRS assessment must be repeated. If the BCVA ETDRS score in the study eye is either >15 letters worse than the previous BCVA ETDRS score or <24 letters score (Cohorts 4 to 7), the surgery must be postponed pending discussion and approval by the Sponsor Medical Monitor.

[redacted]

15. Enrolled subjects will be asked if they are willing to consent to have historical FAF and/or OCT images that were obtained within 1 year prior to enrolment, if available, provided to the sponsor.

Table 3: Follow-up Schedule (Week 72 to Week 240)

Assessment	Local Trial Site[1]					Unscheduled Visit/ Early Termination[2]
	Visit 9 Week 72 (Year 1.5) ±30 days	Visit 10 Week 96 (Year 2) ±30 days	Visit 11 Week 144 (Year 3) ±30 days	Visit 12 Week 192 (Year 4) ±30 days	Visit 13 Week 240 (Year 5) ±30 days	
Standard ophthalmic examination	X	X	X	X	X	X
Colour fundus photography	X	X	X	X	X	X
Fundus autofluorescence	X	X	X	X	X	X
OCT macula	X	X	X	X	X	X
OCT-A[3]	X[4]					X[4]
Fluorescein angiography[3]	X[4]					X[4]
Visual acuity: BCVA/LLVA using ETDRS	X	X	X	X	X	X
Microperimetry	X	X	X	X	X	X
[redacted]						
Additional functional assessments (if required)[6]	X	X	X	X	X	X
AE/SAE monitoring[7]	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
[redacted]						
Submission of historical FAFs and/or OCTs[9]	X					

Abbreviations: AAV2=adeno-associated virus vector serotype 2; AE=adverse event; BCVA=best corrected visual acuity; CFI=complement factor I; CNV=choroidal neovascularisation; ETDRS=early treatment diabetic retinopathy study chart; FA=fluorescein angiography; LLVA=low luminance visual acuity; MNRead=Minnesota low vision reading; OCT=optical coherence tomography; OCT-A=optical coherence tomography angiography; SAE=serious adverse event; [redacted].

1. Dependent upon location and Sponsor approvals, a Surgical Site may also act as a Local Site
2. Minimum study assessments shown; additional assessments may be performed if clinically indicated. [redacted]
3. Other imaging modalities may be performed to assess for CNV if OCT-A is not available. In the event that the OCT/OCT-A images are inconclusive to rule out the presence of CNV the subject will be required to undergo an additional assessment via FA. At the Investigator's discretion, FA may also be performed initially prior to the OCT/OCT-A results being available, but this is not mandatory.
4. OCT-A and/or fluorescein angiography may be performed during the study period if clinically indicated, for example, if a subject converts to wet AMD.

Assessment	Local Trial Site[1]					Unscheduled Visit/ Early Termination[2]
	Visit 9 Week 72 (Year 1.5) ±30 days	Visit 10 Week 96 (Year 2) ±30 days	Visit 11 Week 144 (Year 3) ±30 days	Visit 12 Week 192 (Year 4) ±30 days	Visit 13 Week 240 (Year 5) ±30 days	
[redacted]						
[redacted]						
[redacted]						
7. Additional tests/assessments (i.e., blood tests, imaging or functional assessments) may be conducted, as needed, to allow for safety monitoring.						
[redacted]						
[redacted]						
9. Enrolled subjects will be asked if they are willing to consent to have historical FAF and/or OCT images that were obtained within 1 year prior to enrolment, if available, provided to the sponsor.						

CONTACT NAMES AND ADDRESSES

Sponsor:	Gyroscope Therapeutics Limited
Address:	Rolling Stock Yard, 188 York Way, London, N7 9AS United Kingdom

ABBREVIATIONS

AAV	Adeno-associated virus
AAV2	Adeno-associated virus vector serotype 2
ADA	Anti-drug antibodies
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
AMD	Age-related macular degeneration
AREDS	Age-related Eye Disease Study
ATA	Anti-transgene antibodies
BCVA	Best corrected visual acuity
BSS	Balanced Salt Solution
C3	Complement Component 3
CFI/CFI	Complement Factor I (*Gene*/PROTEIN)
CFP	Colour fundus photography
CMO	Cystoid macular oedema
CNV	Choroidal neovascularisation
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
CS	Complement system
CSR	Clinical study report
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure in utero
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First in Human
GA	Geographic atrophy (also known as macular atrophy)
GCP	Good Clinical Practice
hCFI	Human Complement Factor I
HEK-293	Human embryonic kidney-293
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IRB(s)	Institutional Review Board(s)
IOP	Intraocular pressure
LLVA	Low luminance visual acuity
MAIA	Macular integrity assessment

MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
[redacted]	[redacted]
MP	Microperimeter
N/A	Not applicable
[redacted]	[redacted]
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PSC	Posterior subcapsular
PRL	Preferred retinal locus
PSA	Prostate-specific antigen
REC	Research Ethics Committee
RPE	Retinal Pigment Epithelium
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD-OCT	Spectral domain optical coherence tomography
SDS	Subretinal Delivery System
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
UK	United Kingdom
US	United States
[redacted]	[redacted]
Vg	Vector genomes

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. BACKGROUND INFORMATION AND STUDY RATIONALE

1.1. Age-related Macular Degeneration

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 resulting 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: neovascular AMD and geographic atrophy (GA, also known as macular atrophy) [Chakravarthy 2010]. For the purposes of this protocol, atrophic AMD will be used to reference the late stage population of patients that are classified with GA or advanced dry AMD. There are no approved therapies for atrophic AMD.

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]. Four rare genetic variants of complement factors, involved in the alternative pathway (Complement Factor H, Complement Factor I [CFI], Complement Factor B, and Complement component 3 [C3]) 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 2016]. Another study confirmed these findings and, in addition, showed that low serum CFI levels associated with the presence of rare CFI variants are associated with a much higher risk of development of AMD [Kavanagh 2015]. As CFI serves as a global down-regulator of the alternative pathway [Lachmann 2016], an increase in intra-ocular CFI level has the potential to dampen an over-activated complement system (CS) associated with AMD, reducing the progression of the disease. The subset of GA patients with CFI haploinsufficiency may respond better to treatment. Adeno-associated virus vector serotype 2 (AAV2) vector-based CFI gene transfer (GT005) may have the potential to provide sustained expression of hCFI in AMD patients' eyes.

A more comprehensive review of AMD is provided in the Investigator's Brochure (IB).

1.2. Gene Therapy Medicinal Product

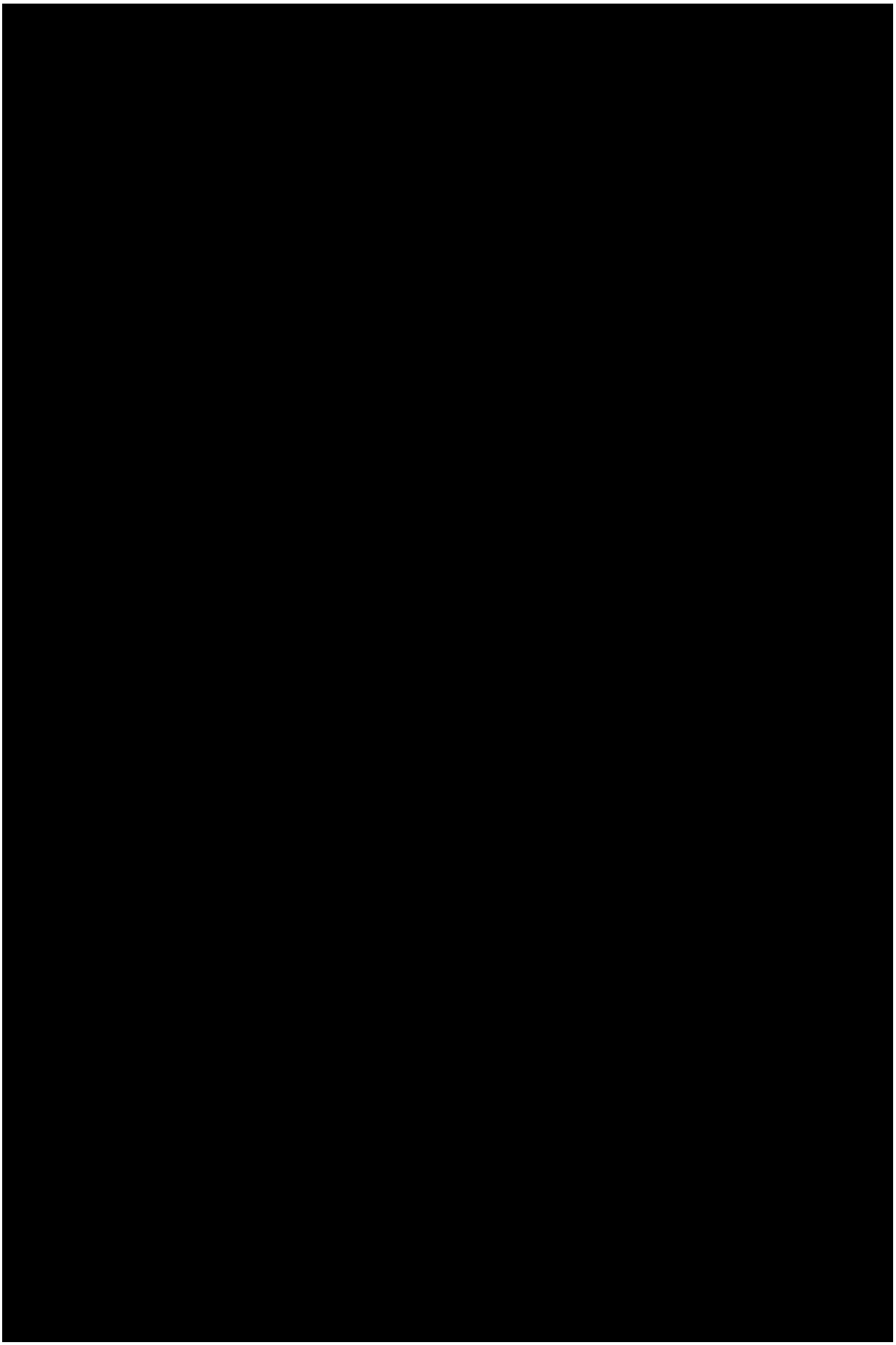
GT005 is a delivery vector comprising a nucleotide sequence encoding *CFI* (rAAV2.CFI). [redacted]

GT005 is supplied as a single vial in an appropriately labelled carton as the secondary container and stored at ≤-60°C.

GT005 can be diluted with formulation buffer which consists of [redacted] Further details regarding GT005 is provided in the IB and Pharmacy Manual.

1.3. Preclinical Data

[redacted]



[redacted]

1.4. Clinical Data

At the time of initiation of this clinical trial, no other clinical studies have been performed using GT005. GT005-01 is a first in human (FIH) study evaluating the subretinal injection to subjects presenting with GA due to AMD.

1.5. Orbit Subretinal Delivery System Medical Device

The Orbit Subretinal Delivery System (SDS) was developed to improve the safety profile of subretinal injections as compared with transvitreal procedure. [redacted]

Further details regarding the Orbit SDS are provided in the Orbit SDS Instructions for Use and the Orbit SDS Surgical Procedure Manual.

1.6. Risks/Benefits

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, to the surgical delivery of GT005, and to the study assessments.

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. [redacted]

[redacted]

The potential risks associated with gene therapy are related to intraocular inflammation, immunogenicity, raised CFI levels, reproductive and developmental risks, and environmental risks as discussed below.

Intraocular Inflammation was not identified as an unexpected or significant risk in the toxicology program [redacted]

[redacted]

Immunogenicity evaluation of the recombinant AAV platform has been extensively used in over 200 clinical trials 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 patients. 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 [FDA 2017; Mingozzi 2013].

[redacted]

Raised CFI levels are expected locally in the retina without impacting the systemic CS. While inhibition of the CS 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] It has also been shown that AAV vectors do not transduce mature sperm [Couto 2004] and, although there is evidence that wild-type AAV2 interferes with mouse embryonic development due to a small DNA sequence containing the P5 promoter inducing developmental arrest, this sequence is absent from recombinant AAV vector genomes [Botquin 1994]. While the risk is expected to be low based on other AAV based gene therapies, eligible subjects participating in the GT005 clinical program are requested to use contraception as per study protocol requirements to minimise the risk of vector transmission.

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 human, animals and the environment. [redacted] No further containment or isolation procedure is required for GT005.

[redacted]

1.6.1.2. Risks Associated with the Surgical and Study Procedure

1.6.1.2.1. Transvitreal Surgery (Cohorts 1 to 4; US and United Kingdom [UK])

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

Intraocular inflammation [redacted]

A **transient visual loss** may be observed in the first days post-surgery due to the bleb related foveal detachment. This can be minimised by avoiding injecting into areas of retinal thinning and by not detaching the fovea, if it is deemed not necessary, and by leaving the contralateral (and best) eye untreated. 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 one month [Xue 2017]. [redacted]

Cataract formation is associated with any vitrectomy procedure. In a published study from [Feng 2014], cataract appeared in approximately 40% of patients following pars plana vitrectomy and resulted in a cataract extraction over the following 2 years. In publicly available safety data, Voretigene Neparvovec, 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 the 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 IOP in 8 of 81 eyes treated (10%). Patients will have IOPs 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 in the study eye 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. [redacted]

1.6.1.3. Suprachoroidal Cannulation Using Orbit Subretinal Delivery System (Cohorts 5 to 7)

Previous generations of the Orbit SDS have been studied in one completed clinical study [Heier 2019] and one on-going study [Banin 2019]. [redacted]

The risks of **intraocular inflammation** and **transient vision loss** and the respective mitigation strategies described in Section 1.6.1.2.1 are identical for the Orbit SDS.

[redacted]

Detailed surgical procedure manuals provided to the sites describe the specifics of the individual procedures.

[redacted]

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 patients with hCFI – a down regulator of the CS – has the potential to dampen an over-activated CS associated with AMD and slow down disease progression. AAV2 vector-based CFI gene transfer (GT005) may have the potential to provide sustained expression of hCFI in patients' eyes with one single injection. Because this is a FIH study, 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 GA extension and ultimately prevent future visual loss.

1.6.3. Risk Benefit Analysis

GT005 is in an early stage of clinical development therefore the potential risks are based on preclinical data and preliminary clinical data 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; FOCUS, NCT03846193]. The main product-related risks are the generation of cellular and/or humoral immune responses to the AAV capsid. Anti-transgene antibody immune responses seen in toxicology studies are considered to be species-specific and are therefore not expected in subjects with lifelong CFI exposure.

The surgical techniques for the subretinal delivery of gene therapy build 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].

[redacted]

Careful pre-dosing assessment and perioperative measures are planned to minimise and monitor any complication of GT005 treatment via either surgical procedure.

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.

1.7. Dose Rationale

[redacted]

[redacted]

[redacted]

1.8. Trial Conduct

This study will be conducted in compliance with the protocol and according to Good Clinical Practice (GCP) and applicable regulatory standards. No deviation from the protocol will be implemented without the prior review and approval of the Research Ethics Committee (REC/Institutional Review Board [IRB]) and Competent Authority except where it may be necessary to eliminate an immediate hazard to a subject. In such a case, the deviation will be reported to the REC/IRB and Competent Authority as soon as possible.

1.9. Population

Subjects with bilateral GA due to AMD in the absence of neovascularisation will be enrolled into the study.

As this is a FIH study, subjects with GA due to AMD and already some vision loss in the study eye have been chosen for Part 1 (Cohorts 1 to 3; dose-escalation). On completion of the dose escalation and review of the safety data by the Data Safety Monitoring Board (DSMB), subjects with better preserved vision, who potentially would be more likely to benefit from treatment, will be entered into Parts 2 (Cohort 4), 3 (Cohorts 5 to 6), and 4 (Cohort 7) of the study.

2. STUDY OBJECTIVES

The overall objectives of the study are to evaluate the safety, dose response and efficacy (anatomical and functional visual outcomes) of three doses of GT005 in subjects with GA due to AMD when delivered subretinally via the transvitreal procedure or suprachoroidal cannulation.

Objectives	Evaluation Criteria
Primary	
• To evaluate the safety of GT005 at 3 doses	• Incidence of ocular and non-ocular treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs) over 48 weeks
Secondary	
• To evaluate long-term safety of GT005 at 3 doses	• Incidence of ocular and non-ocular treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs (TESAEs) up to 240 weeks
• To evaluate the effect of GT005 on anatomical and functional visual outcomes	• Best corrected visual acuity (BCVA) and low luminance visual acuity (LLVA) score via the early treatment diabetic retinopathy study (ETDRS) chart up to 240 weeks • Macular sensitivity as assessed by Mesopic Microperimetry up to 240 weeks • Change in GA area size as assessed by fundus autofluorescence (FAF) up to 240 weeks
• To evaluate the performance of the Orbit SDS (US only)	• Rate of successful delivery of balanced salt solution (BSS) or BSS PLUS to the subretinal space • Rate of successful delivery of GT005 to the subretinal space
• To evaluate the safety of the Orbit SDS (US only)	• Incidence of device-related AEs and SAEs
[redacted]	
• [redacted]	• [redacted]

• [redacted]	• [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted]

3. STUDY DESIGN

3.1. Overall Study Design and Plan Description

This is an open label FIH Phase I/II multicentre study to evaluate the safety, dose response and efficacy of GT005 in subjects with GA due to AMD. The study will be conducted in four parts; Part 1 (Cohorts 1 to 3): dose-escalation, Part 2 (Cohort 4): dose-expansion, Part 3 (Cohorts 5 to 6): dose-escalation with the Orbit SDS, and Part 4 (Cohort 7): dose-expansion with the Orbit SDS.

Parts 1 and 2 (Cohorts 1 to 4) will deliver GT005 via the standard transvitreal procedure and Parts 3 and 4 (Cohort 5 to 7) will deliver GT005 via the Orbit SDS.

The Orbit SDS is a 510(k) cleared device in the US whereby Parts 3 and 4 (Cohorts 5 to 7) will only be used at US sites.

An overview of the study design is provided in [Figure 1: Overview of the Study]. Approximately 65 subjects will be enrolled: up to five in each of Cohorts 1 to 3, up to 20 in Cohort 4, up to five in each of Cohorts 5 and 6, and up to 20 in Cohort 7.

Part 1 (Cohorts 1 to 3; dose-escalation) will test three dose Cohorts ([redacted] vg) of up to five subjects per Cohort. A minimum of three subjects per dose Cohort will be required to evaluate the safety of the respective dose. Sentinel dosing will be applied whereby there will be a minimum of 14 days separation between dosing of the first and second subject of each dose Cohort, to assess any acute reactions to surgery and short-term tolerability to GT005 prior to dosing the remaining subjects in each dose Cohort. Dose escalation will be evaluated by a DSMB and will be assessed based on the Week 5 data for the first three subjects dosed in Cohorts 1 and 2. The DSMB will review the Week 5 safety data for the first three subjects dosed in Cohort 3 prior to dosing in further cohorts. The DSMB can be called upon by the Sponsor to perform safety evaluations as needed.

Subjects will receive a single subretinal injection of GT005 at one of three dose levels:

- Low dose: [redacted]
- Mid dose: [redacted]
- High dose: [redacted]

Part 2 (Cohort 4; dose-expansion) will enrol up to 20 subjects in Cohort 4 with GT005 delivered via the transvitreal procedure to further characterise the safety, dose response and efficacy of GT005. On completion of dose escalation, dose levels determined to be safe and tolerable by the DSMB in Part 1 (Cohorts 1 to 3), may be assessed in Cohort 4. The exact number of subjects that will be enrolled in Cohort 4 will be determined by the Sponsor based on the emerging safety, pharmacodynamic and clinical outcomes data.

Part 3 (Cohort 5 to 6; dose-escalation and evaluation of two doses of GT005 delivered with the Orbit SDS; subretinal delivery via a suprachoroidal cannulation) will enrol three to five subjects at the mid dose ([redacted] vg; Cohort 5) and three to five subjects at the high dose ([redacted] vg; Cohort 6), to evaluate the safety of GT005 treatment when delivered via the Orbit SDS. Part 3 (Cohorts 5 to 6) is independent of, and may be conducted in parallel to, Part 2 (Cohort 4). Dose-escalation will be evaluated by the

DSMB and will be assessed based on the Week 5 safety data for the first three subjects dosed in Cohort 5.

Part 4 (Cohort 7; dose-expansion of GT005 delivered with the Orbit SDS; subretinal delivery via a suprachoroidal cannulation) will enrol up to 20 subjects in Cohort 7 to further characterise the safety, dose response, and efficacy of GT005 treatment when delivered via the Orbit SDS. On completion of dose-escalation, dose levels determined to be safe and tolerable by the DSMB in Part 1 (Cohorts 1 to 3) may be assessed in Cohort 7. The exact number of subjects that will be enrolled in Cohort 7 will be determined by the Sponsor based on the emerging safety, pharmacodynamic and clinical outcomes data.

Analyses of data from the Orbit SDS will be based on data accumulated from US sites.

The study treatment consists of an AAV2 expressing hCFI. The treatment is administered as a single subretinal injection into one eye – "the study eye". Both eyes will be assessed at the screening visit. If both eyes meet the eligibility criteria the study eye will be the worse seeing eye or the eye with the largest GA size for eyes with equivalent visual acuity unless the subject (in consultation with the surgeon) expresses an alternative preference.

The study will, for the individual subjects, consist of up to 13 visits over a 5-year period. 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.

Following consent, subjects will undergo a number of ophthalmic and clinical assessments to determine eligibility for inclusion in the study. Once eligibility is confirmed by the Sponsor, the subject will be enrolled. The subject will be scheduled for surgery [redacted]

Data from subjects screened in another Gyroscope sponsored study at the same Investigative site as FOCUS may be used to fulfil the screening and eligibility requirements for this study. This is only permissible if the screening data are collected within the screening period specified in the clinical protocol. Following consent, subjects will undergo ophthalmic and clinical assessments to determine eligibility for inclusion in the study. Should subjects fail to meet the eligibility for FOCUS, they will be classed as screen failures for this study and may be considered for entry into another Gyroscope sponsored study.

At the screening visit, baseline assessments will be carried out including ophthalmic examination, measurements of the size of GA, retinal examination, microperimetry and visual acuity (BCVA and LLVA). OCT angiography (OCT-A; or other imaging modality if OCT-A is not available) and fluorescein angiography (FA) may be performed at screening to assess presence of occult CNV. In the event, that the OCT/OCT-A images are inconclusive to rule out the presence of CNV, the subject will be required to undergo an additional assessment via FA. At the Investigator's discretion, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory. Blood samples will be taken for safety assessments, genotyping (if required), immunogenicity assessment as well as standard biochemistry and haematology.

Subretinal surgery and administration of GT005 will take place at a surgical site. Additional tests/procedures not specified within the study protocol but required as per the standard practice of the surgical site may be required to be performed either at the local site or the surgical site in preparation for surgery (e.g., electrocardiogram, Methicillin-resistant Staphylococcus aureus test, Snellen BCVA).

[redacted] The surgery will be performed under local anaesthesia. Other anaesthetic options will be considered by the surgeon as appropriate for the subject. Then subjects will receive GT005 at one of the three doses ([redacted]) as a single administration in the form of a subretinal injection of 100 microlitres.

After surgery, subjects will remain in the clinic for up to 24 hours following the surgery to assess any acute issues resulting from the surgery. [redacted]

Subjects will undergo follow-up visits at Week 1, 5 and 8 post-dosing, every three months (at Weeks 12, 24, 36, and 48) for the first year, and at Weeks 72 (1.5 years), 96 (2 years), 144 (3 years), 192 (4 years), and 240 (5 years) post-dosing. At the Week 48 visit, subjects will be invited to consent to the additional follow-up (up to and including Week 240 visit). The Week 48 visit will be the time point used for the primary endpoint of the study. Week 240 (Year 5) will be the end of study visit.

Assessments carried out at the follow-up visits include ophthalmic examination, measurements of the size of GA, retinal examination, microperimetry, visual acuity (BCVA and LLVA) and [redacted] Blood samples will be taken for safety [redacted] (as described in the Schedule of Assessments). [redacted]

If a subject drops out or is withdrawn from the study, prior to the Week 48 visit, every reasonable effort will be made to complete the assessments scheduled for the Early Termination Visit.

If a subject does not agree to consent to long-term follow-up as part of this study, any ongoing AEs will be followed until resolution with subject consent.

4. SUBJECT SELECTION CRITERIA

4.1. Subject Recruitment

Subjects will be recruited from the population of outpatients at the study sites. Potentially eligible subjects interested in taking part in the study may be referred from other sites.

The Investigator will keep records of all subjects screened and included. The reason for screen failure should be stated for all subjects screened but not included. Subjects who are eligible but do not receive treatment with GT005 will be classed as screen failures and may be replaced. The reason for withdrawal should be stated for all subjects included but not completed.

4.2. Inclusion Criteria

For inclusion in the study, subjects must fulfil all of the following criteria:

1. Able and willing to give consent to study participation
2. 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)
3. Cohorts 1 to 6: GA lesion(s) total size in the study eye must be ≥1.25mm^2 and ≤17.5mm^2

   Cohort 7: GA lesion(s) total size in the study eye must be ≥1.25mm^2
4. GA lesion(s) in the study eye must reside completely within the FAF fundus image
5. Cohorts 1 to 3: BCVA of ≤50 letters (6/36 Snellen acuity equivalent or worse) using ETDRS charts in the study eye

   Cohorts 4 to 7: BCVA of ≥24 letters (6/95 and 20/320 Snellen acuity equivalent or better) using ETDRS charts in the study eye
6. Aged ≥55 years
7. Able to attend all study visits and complete the study procedures
8. Women of child-bearing potential need to have a negative urine pregnancy test within two weeks prior to receiving the drug. 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)

4.3. Exclusion Criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. Have evidence or history of CNV in the study eye. Subjects 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

2. Presence of moderate/severe non-proliferative, diabetic retinopathy or worse in the study eye
3. Have history of vitrectomy, sub-macular surgery, or macular photocoagulation in the study eye
4. History of intraocular surgery in the study eye within 12 weeks prior to Screening (Visit 1). [redacted]
5. Have clinically significant cataract that may require surgery during the study period in the study eye
6. Presence of moderate to severe glaucomatous optic neuropathy in the study eye; uncontrolled IOP despite the use of more than two topical agents; a history of glaucoma-filtering or valve surgery is also excluded
7. Axial myopia of greater than -8 diopters in the study eye
8. Have received any investigational product for the treatment of GA within the past 6 months or 5 half-lives (whichever is longer), other than nutritional supplements such as the age-related eye disease study (AREDS) formula
9. Have received a gene or cell therapy at any time
10. Have a contraindication to the specified protocol corticosteroid regimen
11. Are unwilling to use two forms of contraception (one of which being a barrier method) for 90 days post-dosing, if relevant
12. 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
13. 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
14. Cohorts 5 to 7 only: presence of metallic objects or implanted stimulator devices in or near the head, including cochlear implants, deep brain stimulators, vagus nerve stimulators, and other implanted electrodes or stimulators

4.4. Subject Withdrawals

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.

It is important to note that it is impossible for the GT005 product to be removed from the subretinal space after injection. Therefore, once surgery has taken place, subjects can withdraw from the study but cannot withdraw from treatment.

The Investigator also has the right to withdraw subjects from the study (e.g., in the case of non-compliance with the protocol and/or lack of willingness or commitment to co-operate in all phases of the study, or in the case of an AE which is considered intolerable by the subject and/or legal representative). Long-term safety assessment of subjects treated with a gene therapy product is a regulatory requirement and every effort will be made to at least continue monitoring long-term subject safety.

Should a subject decide to withdraw for any reasons, all efforts will be made to complete and report the observations as thoroughly as possible. A complete final evaluation at the time of withdrawal will be performed with an explanation of the exact reason why the subject is withdrawing from the study.

The Investigator is responsible for the optimal individual treatment of the subject.

The Investigator must fill in the “early termination visit” in the electronic case report form (eCRF) explaining all reasons for withdrawal.

If the subject withdraws consent, the Sponsor may retain and continue to use any data collected before withdrawal of consent.

The Investigator will provide or arrange for appropriate follow-up (if required) for subjects withdrawing from the study. After a subject withdraws from the study, the Investigator is still responsible for reporting SAEs considered causally related to the study drug. In addition, the Investigator needs to ensure appropriate treatment and follow-up of each AE still ongoing at the time of the subject’s discontinuation.

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 Ethics Committee. At a minimum it will contain the name of the subject, the Investigator contact number and information regarding the medical treatment received by the subject.

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

4.4.1. Replacements

Subjects who are eligible but do not receive treatment will be classed as screen failures and may 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. Furthermore, subjects with borderline screening assessments (e.g., laboratory parameters) can be re-tested once within the assigned screening period.

In the event, that a subject withdraws from the study for any reason other than an AE or other safety concern or is lost to follow-up within 6 months (Week 24) post-dosing, the subject may be replaced. The reason for the subject’s withdrawal from the study must be recorded.

5. CONCOMITANT MEDICATIONS

5.1. Permitted Concomitant Medications

During the course of the study, subjects will be allowed to continue taking all prescribed and non-prescribed medications, unless excluded as per the study protocol. Note that AREDS based supplements are permitted as no effect on progression of GA has been reported.

[redacted]

Prior to administering the corticosteroid therapy, Investigators must refer to relevant Summary of Product Characteristics (SmPC) and/or label guidance for use.

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.

5.2. Non-permitted Concomitant Medications

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

6. TREATMENT(S)

6.1. Appearance and Content

GT005 is supplied as a single vial containing [redacted] of AAV2 virus vector expressing hCFI.

6.2. Dosage and administration

6.2.1. Dosage

GT005 will be administered at one of three dose levels:

- Low dose: [redacted]
- [redacted]
- [redacted]

6.2.2. Administration

The product is delivered by trained vitreoretinal surgeons as a single administration by subretinal injection under local anaesthesia. Other anaesthetic options will be considered by the surgeon as appropriate for the subject. The injection volume will be 0.1mL.

[redacted]

6.3. Packaging

6.3.1. GT005

GT005 and diluent are both supplied in single vials in an appropriately labelled carton as the secondary container. GT005 and diluent will be stored at ≤-60°C.

6.3.2. Orbit Subretinal Delivery System (US only)

[redacted]

Further details regarding the Orbit SDS are provided in the Instructions for Use and the Orbit SDS Surgical Procedure Manual.

6.4. Labelling

6.4.1. GT005

All study medications will be labelled in accordance with Annex 13: Manufacture of investigational products and specific local requirements.

6.4.2. Orbit Subretinal Delivery System (US only)

All study devices are labelled in accordance with FDA regulations for marketed products. The label contains key elements such as part number, lot number, and expiration date. A label stating, 'For use in clinical trial GT005-01' and site specific information is applied to the shipping container.

6.5. Investigational Medicinal Product Supply Chain

GT005 and diluent will be dispatched directly to sites from either UK or the US approved 3rd party distribution depots.

6.6. Blinding and Randomisation

This is an open label study. All participants will receive GT005.

6.7. Treatment Compliance

GT005 is delivered as a single administration by subretinal injection. The subretinal injection is undertaken by a qualified vitreoretinal surgeon at a 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. Additionally, the Investigator at the surgical site is responsible for ensuring the Orbit SDS is handled in accordance with the relevant Surgical Manual and is only administered to subjects enrolled into the study.

6.8. Drug Storage

GT005 is supplied in a single vial in an appropriately labelled carton as the secondary container and stored at ≤ -60°C.

Prior to administration, GT005 will be thawed at ambient temperature (15 to 25°C). Once thawed, GT005 should be held at ambient temperature and must be administered within the same business day of thaw and preparation. GT005 should be handled as per the Pharmacy Manual.

6.9. Drug and Surgical Device Accountability

GT005 and all applicable surgical devices will only be delivered to the investigational site.

All material supplied is for use only in this clinical study and should not be used for any other purpose.

The Investigator or designee is responsible for GT005 accountability, reconciliation and record maintenance. The Investigator or designated site staff must maintain accountability records throughout the course of the study including records of the amount of GT005 received, the identification of the subject for whom it was dispensed and the date(s) and quantity of GT005 dispensed, and doses and volumes administered.

These records must be available for inspection by a study monitor during the study.

GT005 is a biosafety level 1 product. GT005 post-administration measures regarding destruction and disposal of GT005 and disposables are detailed in the Pharmacy Manual.

The Investigator or designated staff member is responsible for maintaining inventory of the Orbit SDSs used. A record will be kept of the identification of Orbit SDSs, and the identification of the subject for whom the device was used.

At the end of study enrolment, unused and unopened devices should be returned to the Sponsor and recorded in the accountability records. Accountability records must show the identification and quantity of devices returned and method of shipment (US only).

7. STUDY PLAN

The timing and type of assessments required during the study are summarised in the Schedule of Assessments [Table 1: Clinical Schedule (Screening to Week 48); Table 2: Schedule of Visual Tests (Screening to Week 48); Table 3: Follow-up Schedule (Week 72 to Week 240)].

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 the schedule of assessments.

Surgical sites are defined as sites that are approved to participate in this clinical study and to perform the surgical procedure as part of this clinical protocol.

Dependent upon location and Sponsor approvals, a surgical site may also act as a local site. In such cases, all study visits and assessments (as listed in Table 1, Table 2, Table 3) for all timepoints, inclusive of Long-Term Follow-Up, will take place at the surgical site.

7.1. Visit 1 Screening (Day -56 to -1 [-8 weeks]); at Local Site (may be conducted over several days):

The Investigator will explain the study purpose, procedures, and subject responsibilities to each potential study subject. The subject's willingness and ability to meet the protocol requirements will be determined. Prior to any study-specific procedure, written informed consent will be obtained.

The subject will sign and date one copy of the consent form in the presence of the Investigator or his/her designee. The original signed form will be retained at the study site and an additional copy will remain in the subject's medical records; a copy will also be given to the subject.

[redacted]

Data from subjects screened in another Gyroscope sponsored study, conducted at the same Investigative site as the FOCUS study, may be used to fulfil the screening and eligibility requirements for this study. This is only permissible if the screening data are collected within the screening period specified in the clinical protocol. Should subjects fail to meet the eligibility for FOCUS, they will be classed as screen failures for this study and may be considered for entry into another Gyroscope sponsored study (see Section 4.4.1).

After informed consent has been obtained, the subject will be evaluated to determine eligibility. Screening procedures will consist of the following:

Inclusion/Exclusion (screen failures to be recorded), recording of demographics, medical/surgical history and concomitant medication. A urine pregnancy test (only for

women of childbearing potential), vital signs, and AEs will be completed prior to the following procedures:

- Blood draws for:
  - Biochemistry and haematology
  - Serum CFI Levels (central laboratory, baseline measurement only)
  - [redacted]
  - [redacted]
  - Sequencing of complement genes. **Note: this assessment is applicable to all subjects at the Screening Visit <u>unless</u> already completed in another Gyroscope sponsored study.**
  - [redacted]
- Standard Ophthalmic Examination including indirect ophthalmoscopy, a slit-lamp examination, IOP measurement, assessment of anterior chamber and vitreous inflammation, and cataract grading
- Colour fundus photography (CFP)
- FAF
- OCT macula
- OCT-A; if the site does not have OCT-A other imaging modalities may be used to rule out CNV. In the event, that the OCT/OCT-A images are inconclusive to rule out the presence of CNV the subject will be required to undergo an additional assessment via FA
- FA; if OCT/OCT-A images are inconclusive to rule out CNV. FA may also be performed initially prior to OCT/OCT-A results being available, but this is not mandatory
- Microperimetry (assessment can be carried out over two days)

  Note: microperimetry is only applicable at sites with a macular integrity assessment (MAIA) microperimeter
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]

Eligibility assessment and confirmation

Subject eligibility will be confirmed by the Sponsor on the basis of the following criteria:

- GA lesions characteristics assessed by the central reader on the study eye
- BCVA of the study eye
- Investigator statement that the other eligibility criteria are met

The vitreoretinal surgeon will also confirm the study eye.

Subjects whose eligibility is confirmed will be enrolled into the study, assigned a subject number and scheduled for surgery within 8 weeks of screening. The 8-week screening period may be extended up to a maximum of 12 weeks, if agreed by the Sponsor Medical Monitor.

If the screening period is extended past the original 8-week screening period (8–12 weeks), standard ophthalmic exam, haematology/biochemistry, and visual acuity (BCVA/LLVA) assessments should be repeated. In the event, that GT005 administration is deferred during the surgical procedure (e.g., due to an AE occurring during surgery) the screening period may be extended up to 16 weeks if agreed by the Sponsor Medical Monitor. Additionally, if the screening period is extended past 12 weeks (12–16 weeks), in case of GT005 deferral, standard ophthalmic exam, haematology/biochemistry, visual acuity (BCVA/LLVA), and FAFs will be repeated.

Visit 2 will occur at a surgical site. Pre-surgery assessments will include any local requirements of the surgical site. Pre-surgery assessments should be performed within 7 days prior to surgery. The following assessment are also required pre-surgery:

Timing	**Procedure**
Prior to Entering the Operating Room (within 7 days prior to surgery)	• Review of Medical/Surgical History including bleeding history • Vital signs • AE/SAE monitoring • Pre-surgery ocular safety check to verify there are no new ocular AEs that would halt surgery • Microperimetry, if this was omitted at screening, should be performed if feasible • Concomitant medication review including use of anti-thrombotic drugs • [redacted] • Urine pregnancy test (for women of childbearing potential) if the one performed at screening is more than 14 days old • Blood draw for: [redacted] • Visual acuity check: ○ A visual acuity check using ETDRS or 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. If Snellen result is >3 lines (BCVA equivalent to 15 letters) worse than the previous BCVA ETDRS score, then a BCVA with ETDRS assessment must be repeated. If the BCVA ETDRS score in the study eye is either >15 letters worse than the previous BCVA ETDRS score or <24 letters score (Cohorts 4 to 7), the surgery must be postponed

Timing	Procedure
	pending discussion and approval by the Sponsor Medical Monitor.
Within the operating room	[redacted] • Dosing (subretinal injection of GT005) [redacted]

7.2. Visit 2 Day 2 (Post-Operative discharge); at a Surgical Site:

Subjects will be maintained in the clinic for up to 24 hours following the subretinal injection to assess any acute issues resulting from the surgery. The following post dosing assessments will be performed:

About 24 hours after dosing and prior to discharge	• AE/SAE monitoring • Concomitant medication review • Standard ophthalmic examination • OCT macula [redacted] • [redacted] [redacted] [redacted] • Vital signs

The subject will be reminded to use two forms of contraception (one of which being a barrier method) for 90 days for men and women of childbearing potential (see Section 8.3).

7.3. Telephone Call; from a Surgical Site:

Each participant must be contacted by telephone to assess [redacted] and AEs/SAEs within the following week post dosing.

7.4. Visit 3 (Week 1 ± 3 days); at a Surgical Site:

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
- [redacted]
- Standard ophthalmic examination
- OCT macula
- [redacted]
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- BCVA using ETDRS
- [redacted]

7.5. Telephone Call (Week 2 ± 3 days); from a Surgical Site:

Each participant must be contacted by telephone to [redacted] AEs/SAEs 14 days (Week 2) post dosing.

7.6. Visit 4 (Week 5 -7/+3 days); at Local or Surgical Site:

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

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
  - [redacted]
  - [redacted]
  - [redacted]
- Standard ophthalmic examination
- FAF
- OCT macula
- [redacted]

- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- BCVA using ETDRS
- [redacted]
- [redacted]
- [redacted]

7.7. Visit 4.1 (Week 8 ± 7 days); at Local Site or Surgical site:

Recording of: concomitant medication, AEs.

The following procedures will be carried out:

- Standard ophthalmic examination
- Visual acuity (BCVA) using ETDRS
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- [redacted]
- [redacted]

7.8. Visit 5 (Week 12 ± 7 days); at Local Site or Surgical site:

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
  - [redacted]
  - [redacted]
- Standard ophthalmic examination
- CFP
- FAF

- OCT macula
- [redacted]
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Visual Acuity (BCVA and LLVA) using ETDRS
- Microperimetry **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- [redacted]
- [redacted]
- [redacted]

7.9. Visit 6 (Week 24 ± 7 days); at Local Site:

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
  - [redacted]
  - [redacted]
- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory

- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS

[redacted]

7.10. Visit 7 (Week 36 ± 7 days); at Local Site:

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology

[redacted]

- CFP
- FAF
- OCT macula

[redacted]

- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Visual Acuity (BCVA and LLVA) using ETDRS

[redacted]

7.11. Visit 8 (Week 48 ± 7 days); at Local Site:

At this visit subjects will be invited to consent for additional follow-up for up to -5 years post-dosing. If a subject does not agree to consent to long-term follow-up as part of this study, any ongoing AEs will be followed until resolution with subject consent.

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
  - [redacted]
  - [redacted]
- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]
- [redacted]

7.12. Visit 9 (Week 72 ± 30 days); at Local Site:

Recording of: concomitant medication and AEs.

The following procedures will be carried out:

- Standard ophthalmic examination
- CFP
- FAF
- OCT macula

- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]

7.13. Visit 10 (Week 96 ± 30 days); at Local Site:

Recording of: concomitant medication and AEs.

The following procedures will be carried out:

- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

7.14. Visit 11 (Week 144 ± 30 days); at Local Site:

Recording of: concomitant medication and AEs.

The following procedures will be carried out:

- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual Acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.15. Visit 12 (Week 192 ± 30 days); at Local Site:

Recording of: concomitant medication and AEs.

The following procedures will be carried out:

- Standard ophthalmic examination
- CFP
- FAF
- OCT macula

- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]
- [redacted] .
- [redacted]

7.16. Visit 13 (Week 240 ± 30 days); at Local Site:

Recording of: concomitant medication and AEs.

The following procedures will be carried out:

- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]

- [redacted]
- [redacted]

7.17. Unscheduled Visits

7.17.1. Prior to Week 48 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 participant, considering the reason behind the need to arrange an unscheduled visit. These results should be recorded in the subject's medical notes and eCRF.

7.17.2. Post Week 48 to Week 240 Visit

If clinically indicated, subjects may need to return to the site for an unscheduled visit. The following assessments, along with any other assessments that are needed, may be completed at the discretion of the Investigator:

- Recording of AEs and concomitant medication
- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual Acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]

7.18. Early Termination Visit

Subjects have the right to withdraw from the study at any time and for any reason. If a subject refuses to be seen for further visits, the assessments listed in the early

termination visit should be performed at the time they have indicated that they will not attend for further visits.

Where a subject is withdrawn from the study at their own request or based on a decision of the Investigator, follow-up may be maintained, which may include telephone calls or follow-up visits arranged by the investigator, subject to the consent of the participant.

7.18.1. Prior to Week 48 Visit:

In the event that a subject discontinues the study prior to Week 48 visit, the site should use every reasonable effort to ensure that an Early Termination Visit is conducted. The following assessments should be performed:

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
  - [redacted]
  - [redacted]
  - [redacted]
- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]
- [redacted]

7.18.2. Post Week 48 to Week 240 Visit

In the event that a subject discontinues the study after Week 48 and before Week 240 visit, the site should use every reasonable effort to ensure that an Early Termination Visit is conducted. The following assessments should be performed:

Recording of: concomitant medication, vital signs, AEs.

The following procedures will be carried out:

- Blood draw for:
  - Biochemistry and haematology
  - [redacted]
  - [redacted]
  - [redacted]
- Standard ophthalmic examination
- CFP
- FAF
- OCT macula
- [redacted]
- OCT-A if clinically indicated (if a subject converts to wet AMD)
- FA if clinically indicated (if a subject converts to wet AMD). FA is only required if OCT/OCT-A images are inconclusive to rule out the presence of CNV. However, FA may also be performed prior to the OCT/OCT-A results being available, but this is not mandatory
- Microperimetry. **Note: microperimetry is only applicable at sites with a MAIA microperimeter**
- Visual acuity (BCVA and LLVA) using ETDRS
- [redacted]

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical evaluations

8.1.1. Demographics

Race, ethnicity, age (year of birth only), and gender will be captured as demographic data at screening.

8.1.2. Medical History & Concomitant Medication Review

Prior and concomitant medication as well as significant medical history (including all ocular history) will be reviewed and recorded in the eCRF.

This information will comprise (and be updated throughout the study):

- Documentation of presenting complaints and history
- 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
- Current medication use (ocular and other) and those used in past 90 days
- Any drug allergy or contraindication to steroids

8.1.3. 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 five minutes rest in a sitting position for the screening assessment only. The same method should be used throughout the study. Pulse will be assessed as a single measurement.

8.1.4. 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 childbearing potential will undergo urine pregnancy testing at Visit 1 (screening). In case the screening visit and the dosing day is more than 14 days apart, a urine pregnancy test will be repeated before surgery to exclude an early pregnancy.

8.2. Laboratory Evaluations

8.2.1. Clinical Laboratory Evaluations

The anticipated volume of blood samples collected during the study from each subject will not exceed 250 mL (over approximately one year). Any remains from the safety laboratory samples will be disposed of after analyses.

Blood samples for analysis of clinical chemistry and haematology variables will be collected at all specified visits and sent to the central laboratory.

The following safety laboratory variables will be assessed:

Table 5: 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		
	Magnesium		
	Phosphate		
	Potassium		
	Protein Total		
	Sodium		
	Blood Urea Nitrogen		
	Estimated glomerular filtration rate (using CKD-EPI formula)		

8.2.2. Non-standard Assays

[redacted]

Serum CFI Levels

Serum CFI levels will be evaluated using a validated enzyme-linked immunosorbent assay.

Genetic Testing for Complement Genotypes Associated with AMD

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

8.2.3. Ophthalmic Procedures

Standard Ophthalmic Examination

Ophthalmological examinations in both eyes will be performed as follows: anterior segment examination including ocular inflammation assessment via slit lamp

biomicroscopy, IOP via Goldmann applanation tonometry, posterior segment and fundus examination via dilated indirect ophthalmoscopy.

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 (see Section 26.3). Intraocular pressure will be assessed in both eyes with a tonometer.

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. Indirect ophthalmoscopy will be performed per the Schedule of Assessments.

Measurement of Geographic Atrophy

GA area is measured by FAF.

Prior to study start, sites will be qualified by a central reader to ensure fundus images fulfil the appropriate quality requirements. For consistency and to reduce variability, all images will be taken according to a study specific imaging protocol provided to all sites by the reading centre; all images will be reviewed and quantified by a central reader.

The study specific imaging protocol is part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Fundus Autofluorescence

Fundus autofluorescence is a non-invasive retinal imaging modality used in clinical practice to provide a density map of lipofuscin, the predominant ocular fluorophore, in the RPE.

Autofluorescence images of the fundus of both eyes will be obtained using the clinical site's preferred ophthalmic imaging camera. Additional imaging of pertinent retinal regions can be performed at the discretion of the Investigator.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Colour Fundus Photography

Colour images of the fundus of both eyes will be obtained using the clinical site's preferred ophthalmic imaging camera. Additional imaging of pertinent retinal regions can be performed at the discretion of the Investigator.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Optical Coherence Tomography (Macula [redacted])

Optical coherence tomography 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.

A series of horizontal raster scans centred on the fovea of each eye will be obtained with Heidelberg Spectralis (specific setting will be defined in the GT005-01 Photographer Certification, Imaging, & Export Manual.

Additional OCT imaging of pertinent retinal regions of the treated eye may be performed at the discretion of the Investigator.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Optical Coherence Tomography-A

Optical coherence tomography-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. OCT-A may be performed as clinically indicated during the course of the study, for example, if a subject converts to wet AMD.

If OCT-A is not available, other imaging modalities as described in the Central Imaging Manual may be utilised to assess for CNV.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Fluorescein Angiography

A contrast medium (Sodium Fluorescein) is injected into a vein in the subject's arm. The dye travels quickly through the circulatory system and is photographed in black and white as it travels through the eye. The same camera used for fundus photography is employed in this procedure. Two filters are used to limit the image to the colour of light being emitted from the fluorescent dye.

The normal progression of dye is interrupted by diseases of the choroid, retina, and retinal vasculature.

Fluorescein angiography should be performed in the event, that the OCT/OCT-A images are inconclusive in order to rule out the presence of CNV. Fluorescein angiography may also be performed prior to the OCT/OCT-A result being available, however, this is not mandatory.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Microperimetry

Microperimetry, sometimes called fundus related perimetry, is a type of visual field test used to create a "retinal sensitivity map" of the quantity of light perceived in specific parts of the retina in people who have lost the ability to fixate on an object or light source.

The combination of subjective (sensitivity map) and objective (retinography) data will be unified on a microperimetry map, allowing analysis of the retinal function before and after treatment.

As microperimetry is an exploratory assessment it will be included at those sites who have the capability in this study; it is acknowledged that some subjects may not be able to perform this test because of limited ability to fixate.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

Visual Acuity: BCVA and LLVA using the ETDRS chart

The BCVA of each eye will be performed by obtaining the subject's manifest refraction and using the BCVA ETDRS methodology at 4 meters or 1 meter, or level of count fingers, hand motion or light perception.

Low luminance visual acuity should be performed immediately after BCVA and involves placing a 2.0-log-unit neutral density filter over the front of each eye.

Detailed instructions are part of the Investigator Site File.

[redacted]

- [redacted].

[redacted]

Additional functional assessments (microperimetry or standard perimetry)

[redacted]

Additional microperimetry/perimetry should be collected either at the next scheduled visit or at an unscheduled visit if there is no upcoming planned study visit. If a standard perimeter is not available at the site, the Sponsor will assist with arranging transport of the subject to another location to perform the assessment. This additional safety assessment should be acquired at all future study visits (refer to the Central Imaging Manual for specific instructions for functional assessment collection).

8.2.4. Historical FAF and OCT images

If available, historical FAF and/or OCT images obtained within 1 year prior to enrolment will be reviewed by the Central Reading Centre to assess GA lesion size, with the purpose to obtain pre-treatment information on GA growth, to explore the natural history of disease progression.

Enrolled subjects will be asked if they are willing to consent to have historical FAF and/or OCT images that were obtained within 1 year prior to enrolment, if available, provided to the sponsor. This is optional and requires additional consent; the Investigator or designee will explain that the subject is under no obligation to provide this consent. If informed consent is given by a subject, the images will be provided to the Central Reading Centre and the historical lesion size will be measured and recorded.

Detailed instructions are part of the GT005-01 Photographer Certification, Imaging, & Export Manual.

8.3. Contraceptive Requirements

Each subject will be reminded to use two forms of contraception (one of which being a barrier method) for 90 days for men and women of child-bearing potential.

Male subjects

Male subjects whose female partner(s) is (are) pregnant must use a condom from the time of the first administration of treatment or study medication until three months (90 days) following administration of the last treatment or dose of study medication.

If the subject has undergone surgical sterilisation (vasectomy with documentation of azoospermia) a condom must be used.

Male subjects must use acceptable methods of contraception if the male subject's partner could become pregnant from the time of the first administration of treatment or study medication until three months following administration of the last treatment or dose of study medication. The acceptable methods of contraception are as follows:

- Condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Surgical sterilisation (vasectomy with documentation of azoospermia) and a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- The female partner uses oral contraceptives (combination oestrogen/ progesterone pills), injectable progesterone or subdermal implants and a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- The female partner has undergone documented tubal ligation (female sterilisation). In addition, a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository) must be used
- The female partner has undergone documented placement of an intrauterine device or intrauterine system and the use of a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- True abstinence 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

Female subjects

Female subjects of childbearing potential must use medically acceptable methods of contraception from the time of the first administration of treatment or study medication until three months (90 days) following administration of the last treatment or dose of study medication for women of childbearing potential.

Acceptable methods include:

- A documented placement of an intrauterine device or intrauterine device and the use of a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- Documented tubal ligation (female sterilisation). In addition, a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository) should also be used
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Oral contraceptives (combination oestrogen/progesterone pills), injectable progesterone or subdermal implants and the use of a barrier method (condom or occlusive cap (diaphragm or cervical/vault caps) used with spermicidal foam/gel/film/cream/suppository)
- True abstinence 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*

9. ADVERSE EVENT REPORTING

9.1. Definitions

All AEs will be captured from the time the subject provides written informed consent and monitored throughout the study.

Adverse Event: Untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including laboratory abnormal finding), system or disease temporally associated with the use of the medicinal product, whether or not considered as related to GT005.

Adverse Drug Reaction: Untoward and unintended responses to GT005 related to any dose administered.

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression “reasonable causal relationship” means to convey in general that there are facts or evidence meant to suggest a causal relationship.

Serious Adverse Event: Untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing inpatient hospitalisation. Hospitalisation refers to a situation whereby an AE is associated with unplanned overnight admission into hospital.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is a medically significant AE

Adverse Events of Special Interest (AESI): 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. [redacted]

- [redacted]
- [redacted]

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

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

These do not require reporting as AESIs.

Device Specific Adverse Events:

Serious injury means an injury or illness that:

1. Is life-threatening,
2. Results in permanent impairment of a body function or permanent damage to a body structure, or
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

For the reporting purposes of this study, a serious injury related to the device is considered an SAE.

9.2. Expectedness

An expected adverse reaction is where the nature or severity of the AE is consistent with the applicable product information (IB for an unapproved investigational product or SmPC or approved Package Insert for an authorised product), otherwise it is considered unexpected.

9.3. Intensity of Adverse Event

The Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- 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

9.4. Causality Assessment

When assigning relatedness of the AE, consideration will be given to whether there is a plausible relationship to either the study medication or the surgical procedure. For Cohorts 4 to 7, AEs deemed related to the surgical procedure will be considered to be related to either the transvitreal procedure or to the suprachoroidal cannulation procedure with the Orbit SDS, depending on the route of GT005 administration. AEs related to the suprachoroidal cannulation procedure with the Orbit SDS are considered device -related events.

AE severity and relationship to the study medication or the surgical procedure will be assessed at the site by the Investigator or a medically qualified designee.

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, mechanics of surgical procedure) to assume a causal relationship to the study medication 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 study medication or the surgical procedure with GT005 administration.

Unknown: there is insufficient information to assess plausibility of causal relationship to the study medication or the surgical procedure.

9.5. Action Taken Regarding the Study Drug

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

- Dose not changed – no action taken
- Drug withdrawn – not administered
- Dose reduced – partially administered
- Unknown/not applicable

9.6. Outcome

Each AE must be rated by selecting one of the following:

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

9.7. Recording Adverse Events

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious).

All AEs occurring during the study must be documented on the appropriate section of the eCRF.

If an AE is considered serious, it must also be recorded on the Serious Adverse Event Form provided separately.

9.8. Reporting Serious Adverse Events and Adverse Events of Special Interest to the Sponsor

All AESIs and SAEs occurring from informed consent through to the long-term follow-up section of the study, or if the subject is not taking part in the long-term follow-up part of the study, until resolution of the event will be reported immediately (within 24 hours) by the Investigator, Contract Research Organisation (CRO) and/or Sponsor to the [redacted] Safety team, regardless of causal relationship. The applicable form (electronic data capture or back-up form) must be filled in by a member of the research team and kept in the Investigator site file.

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 – United States:***

Telephone: [redacted]

Fax: [redacted]

e-mail: [redacted]

OR

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

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]***, dial 3 (United States)***

OR

[redacted] ***(Europe)***

A pregnancy is not considered to be an AE or SAE; however, it must be reported to Medpace Clinical Safety within 24 hours of knowledge of the event. Medpace 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 Medpace Clinical Safety. 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.

Gyroscope Therapeutics will report all relevant safety information about suspected unexpected serious adverse reactions (SUSARs) (and any new safety information that would adversely affect the safety of subjects or the conduct of the study) for the product under investigation to the Competent Authorities, Institutional Review Boards (IRBs)/Research Ethics Committee (RECs), Investigators and DSMB for the duration of the study as required by country-specific regulations.

In addition, any new safety information that would adversely affect the safety of subjects or the conduct of the study will be reported by Gyroscope to the Competent Authorities, Research Ethics Committees (RECs), DSMB and Investigators. If the study is to be suspended as a result of a SUSAR, or due to any urgent safety measure taken, Competent Authorities and RECs will be notified as soon as possible and within three days of the decision.

For study centres in the United States, Investigational New Drug safety reports will be submitted directly to the Investigators. It is the Investigators' responsibility to notify their IRBs/RECs in a timely manner. Gyroscope will submit Safety Reports to the applicable Competent Authorities and IRBs/RECs as required by country-specific regulations.

[redacted]

[redacted]

10. DATA MANAGEMENT

Data will be recorded on an eCRF by the Investigator (or designee). The database, data entry and electronic checks will be developed using a Clinical Database Management System. Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency and completeness of the data. An electronic audit trail system will be used to track all data changes in the database.

Data clarification queries will be generated electronically in order to clarify any issues which arise regarding the data entered into the eCRF and database.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary; medications will be coded using the World Health Organisation Drug Dictionary.

10.1. Trial Documentation and Trial Confidentiality

10.1.1. Trial Documentation, eCRFs and Document Keeping

The Investigator must generate and maintain adequate records (subject medical records, eCRFs, source documents) to enable the conduct of this study to be fully documented. Each subject enrolled into the study must have an eCRF completed and the eCRF must be reviewed and signed off by the Investigator. This applies to those subjects who failed to complete the study (even during the pre-surgery period). eCRFs are to be completed either at the time of the subject's visit or as soon as possible after the visit so that they always reflect the latest observations on the subjects participating in the study. The Investigator must verify that all data entries in the eCRFs are accurate and correct. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the investigational staff and are accessible for verification by the clinical monitor. If electronic records are maintained, the method of verification must be discussed with the investigational staff. A source data verification log will be prepared by the CRO. This will describe the proportion of eCRF data that will be verified by the monitor against the subjects' medical records and source data.

The Sponsor recommends that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

If data are recorded directly into the eCRF, there should be, at a minimum, an entry in the medical record that each of the assessments was performed; who performed it and the date it was done.

The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible Investigator or an authorised member of the investigational staff.

Data clarification and query resolution will be conducted on an ongoing basis by the monitor and the contract data management company. The Sponsor will have overall responsibility for the data.

The Investigator must be aware of their responsibility to retain subject identification codes in line with regulatory requirements after completion or discontinuation of the

study. If a subject withdraws from the study, then the reason must be noted in the eCRF. If a subject ceases treatment because of an AE, reasonable efforts must be made to clearly document the outcome.

The Investigator will allow authorised Sponsor personnel, auditors and regulatory authorities direct access to the subjects' medical records.

Copies of protocols, eCRF page/printouts, originals of test results, reports, drug dispensing logs, correspondence, records of informed consent or other documents pertaining to the conduct of the study must be kept on file by the Investigator in line with regulatory requirements or for the period of time specified by local law for the preservation of hospital subject documents, whichever is longer. No study documents should be destroyed without prior written agreement between the Sponsor and the Investigator. Where storage at the centre is limited, the Sponsor may make arrangement for documents to be stored at an independent data archiving facility on behalf of the Investigator. Should the Investigator wish to assign the study records to another party, or move them to another location, the clinical trial monitor must be consulted.

10.1.2. Confidentiality of Trial Documents and Subject Records

The Investigator must ensure the subjects' anonymity is maintained. On eCRFs or other documents submitted to the Sponsor (or designee), subjects must NOT be identified by their names but by an identification code (usually their study number). The Investigator will be responsible for maintaining a separate log of subjects' codes, names and unique identifiers. This log will be maintained as required by applicable regulatory requirements. Documents not for submission to the Sponsor or designee, e.g., subjects' written consent forms, must be maintained by the Investigator in strict confidence. Genetic testing will occur prior to surgery but to ensure subject confidentiality, the distribution of these data will be carefully controlled.

11. STATISTICAL ANALYSIS PLAN

A detailed statistical analysis plan (SAP) will be produced after having finalised the protocol and before the database is locked prior to analysis.

11.1. Sample Size

As this is a FIH exploratory Phase I/II study, no formal sample size has been calculated.

11.2. Population for Analysis

Two analysis sets will be defined. The Safety Analysis Set (SAF) will include all subjects who have undergone surgery and received GT005. The SAF will be used for analysis of safety and laboratory data. The Full Analysis Set (FAS) will include all subjects in SAF who have baseline and at least one post-baseline value of GA area size via FAF in the study eye. The FAS will be used for analysis of efficacy data.

11.3. Statistical Analysis

The detailed statistical analyses will be outlined in the SAP.

The main analysis will be performed at the conclusion of the study (Week 240), after which a clinical study report (CSR) will be prepared. 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. Additionally, a safety focused analysis will be conducted to enable the independent data review by a DSMB after three subjects in Cohorts 1 to 3 and Cohort 5 have completed the 5-week post-surgery visit. Additional DSMB meetings may be held as needed or as requested by the DSMB members. Full details can be found in the DSMB Charter.

Analyses of data involving the Orbit SDS is US-specific.

For the main statistical analysis and CSR, all efficacy (anatomical and functional visual outcomes) and safety data will be listed and summarised using descriptive statistics by dose and route of administration, and by assessment (Visits 1 to 8). The Long-term follow-up data (Visits 9 to 13) will be reported separately using descriptive statistics by dose and route of administration and by assessment. Additionally, for all ocular evaluations and tests, and ocular AEs, where appropriate these will be additionally presented by eye (Treated [Study Eye]/Untreated [Fellow Eye]). The descriptive summary for the categorical variables will include subject counts (n) and percentages and, if appropriate, frequency of events. The descriptive summary for the continuous variables will include counts (n), means, medians, standard deviations and minimum and maximum values. Where possible, all data from subjects who withdraw prematurely from the study will be included in any presentations. Further details on the handling of withdrawals and/or missing data will be specified in the SAP.

Subgroup analyses will be performed, if appropriate, to evaluate some of the efficacy endpoints across subgroups defined by genetic classification: e.g., a rare variant resulting in CFI haploinsufficiency and those without.

[redacted]

Graphical displays appropriate to the types of data may be used to present any important findings.

Any deviations from the planned analyses detailed in the protocol will be documented in the SAP and final CSR. If the study is prematurely discontinued, all available data will be listed and a review will be carried out to determine which statistical analyses are considered appropriate.

11.3.1. Demographics and Baseline Characteristics:

Surgical details and measures at baseline including: demographics, medical/surgical history, concomitant medication, laboratory safety, and urine pregnancy testing will be summarised descriptively by dose and route of administration. No formal comparisons between Cohorts will be made. Assessments made at screening/baseline and also post-surgery will only be included in their respective safety and efficacy tables, together with post-baseline assessment values.

A medication given prior to the injection of study drug during surgery will be classified as a prior medication. A medication given with or after the injection of study drug will be classified as concomitant. Prior medications continuing during the study will be labelled accordingly in the listings.

Verbatim medical/surgical history terms will be coded (to preferred terms) using terminology from MedDRA. Medications will be coded using the World Health Organisation Drug Dictionary to Anatomical Therapeutic Chemical classification level 2 (therapeutic main group) and preferred term.

Additionally, the last visual acuity values measured using the BCVA ETDRS prior to surgery will be presented with the baseline data by dose and route of administration and by eye (Treated [Study Eye]/Untreated [Fellow Eye]). Genetic testing will also occur prior to surgery but to ensure subject confidentiality, the distribution of these data will be carefully controlled. Further details of the procedures required for maintaining the subject's genetic profile confidentiality will be discussed in greater detail in the SAP.

11.3.2. Efficacy

Efficacy assessments to evaluate the anatomical and functional visual outcomes involve: GA area size (via FAF), [redacted], macular mean sensitivity via Microperimetry, [redacted] For continuous efficacy variables the change from baseline will be derived and presented together with actual values over time (visit) by dose and route of administration and by eye (Treated [Study Eye]/Untreated [Fellow Eye]). Categorical variables from any ocular evaluations will be presented by classification over time (visit) by dose and route of administration and by eye (Treated [Study Eye]/Untreated [Fellow Eye]).

[redacted]

The GA area size data will be compared to historical data on natural disease progression, including pre-treatment data from FOCUS subjects if available.

[redacted]

11.3.4. Safety

The assessment of safety will be based primarily on the following: AEs, ophthalmic examination, BCVA/LLVA scores (ETDRS), vital signs, laboratory safety (biochemistry and haematology), and [redacted] Adverse Events

Adverse events will be collected and recorded throughout the study and verbatim AE terms will be coded (to preferred terms) using terminology from MedDRA.

A TEAE is defined as an AE that is first identified, or is identified to worsen in intensity, on or after the subject receives the study medication during surgery.

The incidence, maximum intensity, and relationship to study medication or procedure of TEAEs will be summarised by system organ class and preferred term, according to dose and route of administration, as appropriate, and classified as systemic or ocular (Treated [Study Eye]/Untreated [Fellow Eye] or Both eyes).

All AEs, SAEs, AESIs, AEs leading to discontinuation, and deaths will be listed.

11.3.4.1. Ophthalmic Examination

Ophthalmic examinations will be displayed as continuous (actual and change from baseline values), or categorical data as appropriate by dose and route of administration, and by eye (Treated [Study Eye]/Untreated [Fellow Eye]) for each assessment. For continuous data evaluations, differences and change from baseline differences between Treated and Untreated eyes will also be presented by dose and route of administration for each assessment.

11.3.4.2. Visual Acuity (BCVA and LLVA)

Will be presented as for continuous ophthalmic examinations by eye.

11.3.4.3. Laboratory Tests

For haematology and chemistry laboratory test results, descriptive statistics and change from baseline over time will be summarised by dose and route of administration. All laboratory test results including urinalysis will be listed.

11.3.4.4. Vital Signs

For blood pressure and pulse rate, and body temperature, descriptive statistics and change from baseline over time will be summarised by dose and route of administration.

[redacted]

12. INSTITUTIONAL REVIEW BOARD (IRB)/ RESEARCH ETHICS COMMITTEE (REC)

This study must be conducted in compliance with IRBs/RECs, informed consent regulations, the Declaration of Helsinki, International Council for Harmonisation (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 IRB/REC 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 IRB/REC that they comply with GCP requirements. The IRB/REC approval must identify the protocol version as well as the documents reviewed.

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

The Investigator should provide written reports to the REC annually or more frequently if requested on any changes significantly affecting the conduct of the study and/or increasing risk to the subjects.

13. REGULATORY REQUIREMENTS

The study will be authorised by the Competent Authority.

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

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

14. PROTOCOL AMENDMENTS

14.1. 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 IRB/REC, 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, this 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 IRBs/RECs or Competent Authority 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 GT005 used in the study

Substantial amendments must be notified to the IRB/REC and Competent Authority. Prior to implementation, documented approval must be received from the IRB/REC.

- **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 IRB/REC and Competent Authority notification, forthwith

14.2. 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 the electronic data capture (EDC) system. Protocol deviations must be reported to Competent Authority and the IRB/REC as per their 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 IRB/REC, 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.

15. INFORMED CONSENT

It is the responsibility of the Investigator to obtain written consent from each subject, or from the subject's legal representative prior to any study related procedures taking place.

If the subject and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the subject.

Consent must be documented by the subject's dated signature. The signature confirms that the consent is based in information that has been understood. Moreover, the Investigator must sign and date the informed consent form.

Each subject's signed informed consent must be kept on file by the Investigator. One copy must be given to the subject.

16. DIRECT ACCESS TO SOURCE DOCUMENTATION/DATA

The Investigator must permit study-related monitoring, audits, IRB/REC review or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

It is understood that the independent study monitor(s) will contact and visit the Investigator/clinical site before the study, regularly throughout the study and after the study has been completed. At these visits the monitor(s) will inspect various study records; eCRFs, Investigator Site File and source data, provided that subject confidentiality is respected. The Investigator and/or site staff will be expected to be available if requested by the monitor.

18. QUALITY ASSURANCE

The Sponsor may perform an audit at any time according to the Sponsor's Standard Operating Procedure in order to verify whether the study is being conducted according to GCP.

19. INSURANCE

Appropriate insurance cover has been secured in favour of subjects participating in clinical studies. The cover is provided to the subject on terms and conditions of the clinical trial insurance. Insurance cover exists for health damages resulting from measures carried out in connection with the clinical study.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and appointed staff. No study material may be disclosed to any party not directly involved in the study without written permission from the Sponsor.

The Investigator must assure that subject's anonymity will be provided. The Investigator will keep a separate list with at least the initials, the subject's study number, names, addresses and telephone numbers. The Investigator will maintain this for as long as requested by the Sponsor.

21. PREMATURE TERMINATION OF THE STUDY

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.

All subjects participating in the clinical study will receive from the Investigator an alert card, which has been previously agreed by the Sponsor and approved by the IRB/REC, containing at minimum the name of the subject, the Investigator contact number and information regarding the medical treatment received.

Where follow-up after the end of the study is required, in particular when this occurs over a long-term, the Sponsor will ensure that there is a process in place for follow-up of the subjects treated with the product even in cases where the product development is discontinued or the (former) Sponsor ceases to exist as a legal entity.

This process will be achieved by:

- Appropriate information about follow-up of the subjects after the end of the clinical study provided to healthcare establishments that served as centres for the particular clinical study
- Websites/phone-lines that provide data/consultation in case of complications
- Subject alert cards that inform treating physicians about the product used, and any independent registries or other sources of data available in case of safety/efficacy issues, and of the need to inform the national Competent Authority, the investigational sites and the Sponsor in the event of certain serious adverse reactions. These alert cards should contain at minimum the name of the subject, a physician contact number and information regarding the medical treatment received. They should have been previously agreed by the Sponsor and approved by the IRB/REC. This may be the same as the one used for the clinical study if changes or additional information is not required to address further follow-up after the end of the study

22. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be securely archived by the Investigator in a secure study file.

Essential documents must be retained for at least thirty years after clinical use. It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the institution.

23. PUBLICATION OF RESULTS

No information provided by the Sponsor to the Investigators, DSMB or Study Steering Committee members for the purposes of performing or monitoring the study, will be published, or passed on to a third party, without prior written approval by the Sponsor.

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

24. STUDY COMMITTEES

24.1. DATA SAFETY MONITORING BOARD

Composition

A DSMB will be formed to review all safety data at predetermined intervals during the study. Additional DSMB meetings may be held as needed or as requested by the DSMB members. The DSMB will comprise of at least three individuals who cumulatively have the clinical and medical expertise to monitor the safety of subjects in the clinical study and will include a minimum of one clinician expert in the management of AMD and clinical immunology. The DSMB will be chaired by one of the clinical experts who will attend all meetings. No DSMB member will be an Investigator in this study.

Roles and Responsibilities of DSMB

The roles and responsibilities of the DSMB are defined in the DSMB Charter, which include, but are not limited to:

- Monitoring and reviewing all safety issues relative to the conduct of the study
- Ensuring the protection and safety of subjects participating in the study
- Recommending dose escalation in accordance with available safety data and study stopping rules
- Recommending a different BCVA threshold for entry into the study
- Providing recommendations to continue, modify the design, suspend or terminate the study depending upon emerging safety data
- Communicating other recommendations or concerns as appropriate

Dose Escalation

- The DSMB will meet after the third subject has been enrolled (recruitment and treatment will continue – there will be no study hold) and provided Week 5 data in Cohorts 1 to 3, and in Cohort 5
- If treatment has been tolerated and stopping rules have not been met, the DSMB will recommend to Gyroscope that enrolment of the next study Cohort can commence
- Screening of potential subjects will be allowed prior to the DSMB meeting and decision, but treatment must not be administered to subjects in the higher dose group until the outcome of the DSMB recommendation has been provided in writing to Gyroscope

Change to Inclusion Criteria

The DSMB will meet after the third subject has been enrolled (recruitment and treatment will continue – there will be no study hold) and the possibility of raising the BCVA threshold for inclusion in the study at the respective dose-level will be assessed based on Week 5 safety data for the first three subjects dosed in Cohorts 1 and 3.

DSMB Stopping Rules

The DSMB will review the study data and recommend stopping dose escalation if any toxicity is evident within five weeks (Visit 4) of treatment, that is considered related to study medication or route of administration and that has:

- Significantly and/or likely permanently reduced the subjects remaining vision
- Been life-threatening
- Occurs in one or more subjects in the same Cohort and would be considered severe enough to outweigh the potential benefits of the study medication

In addition to the prescheduled meetings, the DSMB may be called upon at any time during the study to review immediate safety outcomes and/or concerns as they arise.

Details regarding the DSMB mission and content of the DSMB data safety reviews will be specified in the DSMB charter.

25. REFERENCES

Access Economic Report 2010. The Global Economic Cost of Visual Impairment. Report by Access Economics Pty Limited for AMD Alliance International.

Anderson. D. H, Radeke. M. J, Gallo, N. B, et al. The pivotal role of the complement system in aging and age-related macular degeneration: Hypothesis re-visited. Progress in Retinal and Eye Research 2010; 29: 95-112.

Banin E. Abstract PA03: "Phase 1/2a Study of Subretinally Transplanted Human Embryonic Stem Cell-Derived RPE Cells in Advanced Dry-Form AMD Patients". American Academy of Ophthalmology Annual Meeting 14-Oct-2019.

Botquin, V., Cid-Arregui, angel, and Schlehofer, J.R. Adeno-associated virus type 2 interferes with early development of mouse embryos. J. Gen. Virol. 1994; *75*, 2655–2662.

Chakravarthy. U, Wong. T.Y, Fletcher. A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmology 2010, 10:31.

Chang S. LXII Edward Jackson lecture: open angle glaucoma after vitrectomy. Am J Ophthalmol. 2006;141(6):1033-1043.

Chew E, et al. Evaluation of the Age-Related Eye Disease Study Clinical Lens Grading System AREDS Report No. 31. Ophthalmol 2010; 117: 2112–2119.

Couto, L., Parker, A., and Gordon, J.W. Direct Exposure of Mouse Spermatozoa to Very High Concentrations of a Serotype-2 Adeno-Associated Virus Gene Therapy Vector Fails to Lead to Germ Cell Transduction. Hum. Gene Ther. 2004; *15*, 287–291.

FDA Briefing Document, Advisory Committee Meeting, October 12, 2017, BLA 125610, Voretigene Neparvovec, Spark Therapeutics, Inc. (FDA Website)

Feng H, Adelman RA .Cataract formation following vitreoretinal procedures. Clinical Ophthalmology Volume 2014:8 Pages 1957—1965

Ferris. F. L, Wilkinson. C. P, Bird. A, et al. Clinical Classification of Age-related Macular Degeneration. Ophthalmology 2013; 120 (4): 844-851.

Fritsche. L. G, Igl. W, Cooke Bailey. J. N, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nature Genetics 2016; 48 (2): 134-143.

Ginn, S.L., Amaya, A.K., Alexander, I.E., Edelstein, M., and Abedi, M.R. (2018). Gene therapy clinical trials worldwide to 2017: An update. J. Gene Med. *20*, e3015.

Gleeson. P.J, Wilson, V, Cox. T.E, et al. Chromosomal rearrangement—A rare cause of complement factor I associated atypical haemolytic uraemic syndrome. Immunobiology 2016; 221; 1124–1130

Heier J. S, Kherani S, Desai S, et al. Intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial. Lancet. 2017; 390(10089): 50-61.

Heier J. S, Ho A.C, Samuel M.A, et al. Safety and Efficacy of Subretinally Administered Palucorcel for Geographic Atrophy of Age-related Macular Degeneration: Phase 2b

Study. Ophthalmology Retina. 2019 In Press: DOI: https://doi.org/10.1016/j.oret.2019.11.011

Jonasson. F, Fisher. D. E, Eiriksdottir. G, et al. Five-year incidence, progression and risk factors for age-related macular degeneration: The Age, Gene/Environment Susceptibility Study. Ophthalmology. 2014; 121(9): 1766–1772.

Kavanagh. D, Yu. Y, Schramm. E, et al. Rare genetic variants in the *CFI* gene are associated with advanced age-related macular degeneration and commonly result in reduced serum factor I levels. *Human Molecular Genetics*, 2015, Vol. 24, No. 13 3861–3870

Kersey, J., Broadway, D. Corticosteroid-induced glaucoma: a review of the literature. *Eye* 2006; 20, 407–416.

Lachmann. P. J, Lay. E, Seilly. D. J, et al. Further studies of the down-regulation by Factor I of the C3b feedback cycle using endotoxin as a soluble activator and red cells as a source of CR1 on sera of different complotype. Clinical and Experimental Immunology 2016; 183: 150–156.

MacLaren. R.E, Groppe. M, Barnard. A.R, et al. Retinal Gene Therapy in Patients with Choroideremia: Initial Findings from a Phase 1/2 Clinical Trial. Lancet 2014; 383 (9923): 1129–1137.

Mandava, N., Tirado, V., Geiger, M., Patnaik, J., Frazer-Abel, A., Lynch, A., Mandava, N., Palestine, A., Holers, M., Wagner, B., et al. (2019). A0180: Plasma and Vitreous Complement Levels in Humans with Proliferative Diabetic Retinopathy.

Mingozzi, F., and High, K.A. Immune responses to AAV vectors: overcoming barriers to successful gene therapy. Blood 2013; 122, 23.

NIH: Age-related macular degeneration. National Eye Institute. June 2015. Available from: https://www.nei.nih.gov/learn-about-eye-health/resources-for-health-educators/eye-health-data-and-statistics/age-related-macular-degeneration-amd-data-and-statistics [Last accessed: February 2020].

Provost N, Le Meur G, Weber M, et al. Biodistribution of rAAV vectors following intraocular administration: evidence for the presence and persistence of vector DNA in the optic nerve and in the brain. Mol Ther. 2005;11(2):275-83.

Russell. S, Bennett. J, Wellman. J.A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet 2017; http://dx.doi.org/10.1016/S0140-6736(17)31868-8.

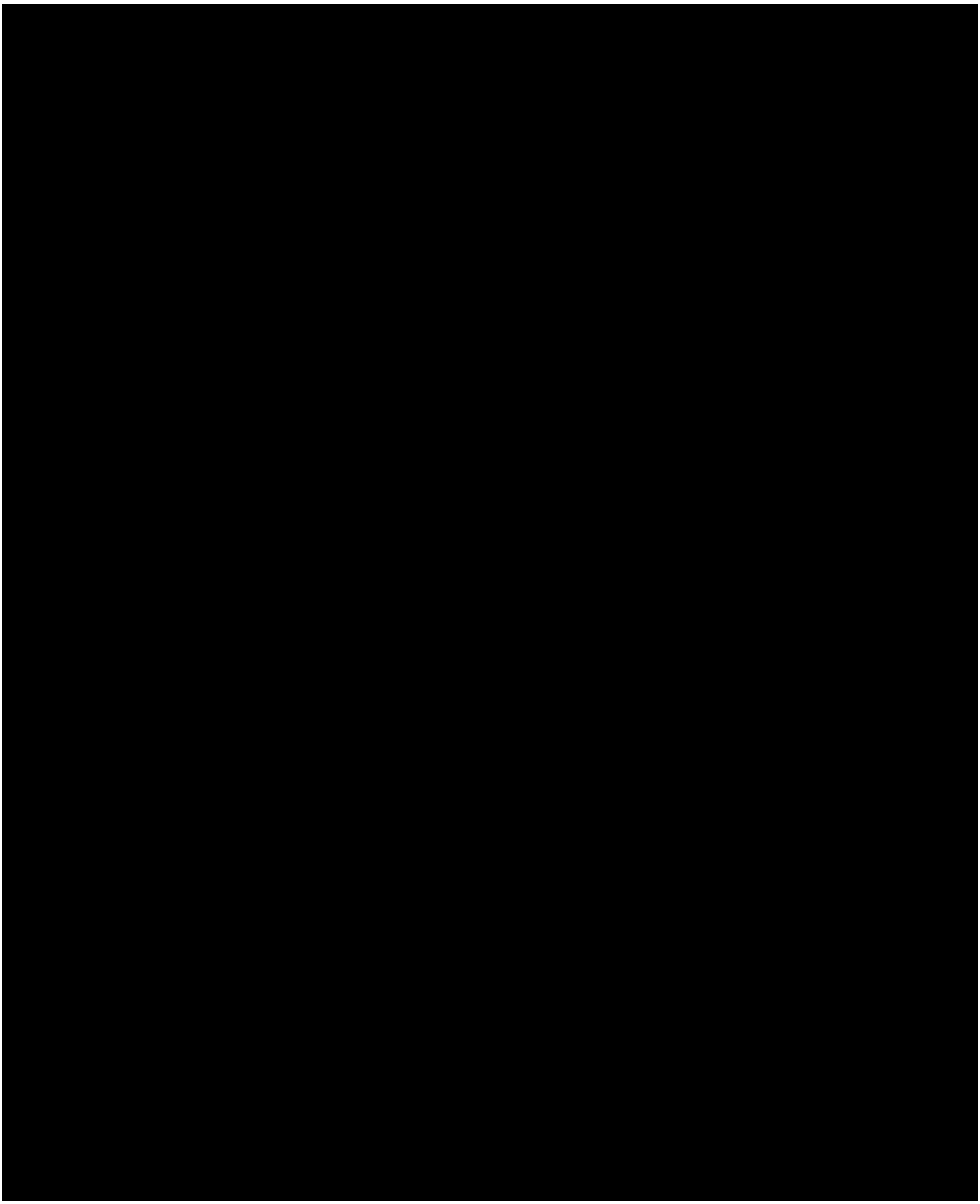
www.clinicaltrials.gov. NCT03846193. Available from: https://clinicaltrials.gov/ct2/show/NCT03846193?term=GT005-01&draw=2&rank=1 [Last accessed: Jan, 2022].

Xue K, Groppe M, Salvetti AP and MacLaren RE. Technique of retinal gene therapy: delivery of viral vector into the subretinal space. Eye (2017) 31, 1308–1316.

26. APPENDICES

26.1. Early Treatment Diabetic Retinopathy Study Scale - Example

[redacted]



26.3. AREDS Clinical Lens Grading System

Overview

The 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 centre 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 centre. 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.

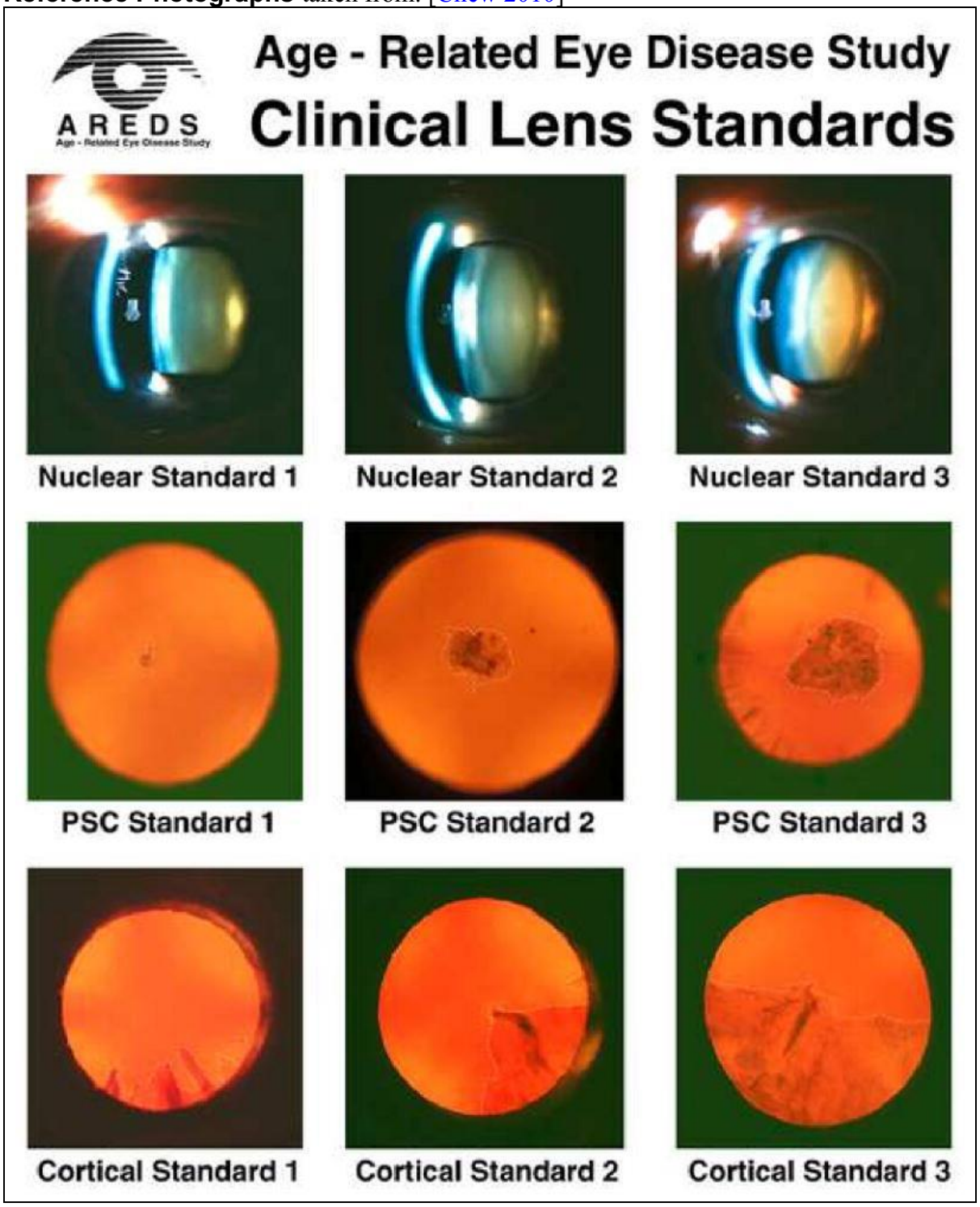
PSC Standard 3 shows a roundish opacity that is even larger and involves the centre of the lens. (An array of cortical spokes, located peripherally between 6:30 and 10:00 and rather unfocused, is not considered part of PSC.)

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]



26.4. Declaration of Helsinki

Recommendations Guiding Medical Physicians in Biomedical Research Involving Human Volunteers
Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975 and the 35th World Medical Assembly, Venice, Italy, October 1983 and revised 41st World Medical Assembly Hong Kong, 1989 and by the 48th World Medical Assembly, South Africa, October 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.
The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".
The purpose of biomedical research involving human volunteers must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.
In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.
Medical progress is based on research which ultimately must rest in part on experimentation involving human volunteers.
In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person volunteered to the research.
Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human volunteers. They should be kept under review in the future.
It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

Biomedical research involving human volunteers must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
The design and performance of each experimental procedure involving human volunteers should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the Sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Biomedical research on human volunteers should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person.
The responsibility for the human volunteer must always rest with a medically qualified person and never rest on the volunteer of the research, even though the volunteer has given his or her consent.
Biomedical research involving human volunteers cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the volunteer.
Every biomedical research project involving human volunteers should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the volunteer or to others. Concern for the interest of the volunteer must always prevail over the interests of science and society.
The right of the research volunteer to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the volunteer and to minimise the impact of the study on the volunteer's physical and mental integrity and on the personality of the volunteer.
Physicians should abstain from engaging in research projects involving human volunteers unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports on experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
In any research on human beings, each potential volunteer must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the volunteer's freely-given informed consent, preferably in writing.
When obtaining informed consent for the research project the physician should be particularly cautious if the volunteer is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the volunteer is a minor, permission from the responsible relative replaces that of the volunteer in accordance with national legislation.
Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (CLINICAL RESEARCH)

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.
The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient

III. Non-Therapeutic Biomedical Research Involving Human Volunteers (NON-CLINICAL BIOMEDICAL RESEARCH)

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
The volunteer should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the volunteer.

[redacted]

[redacted]

[redacted]

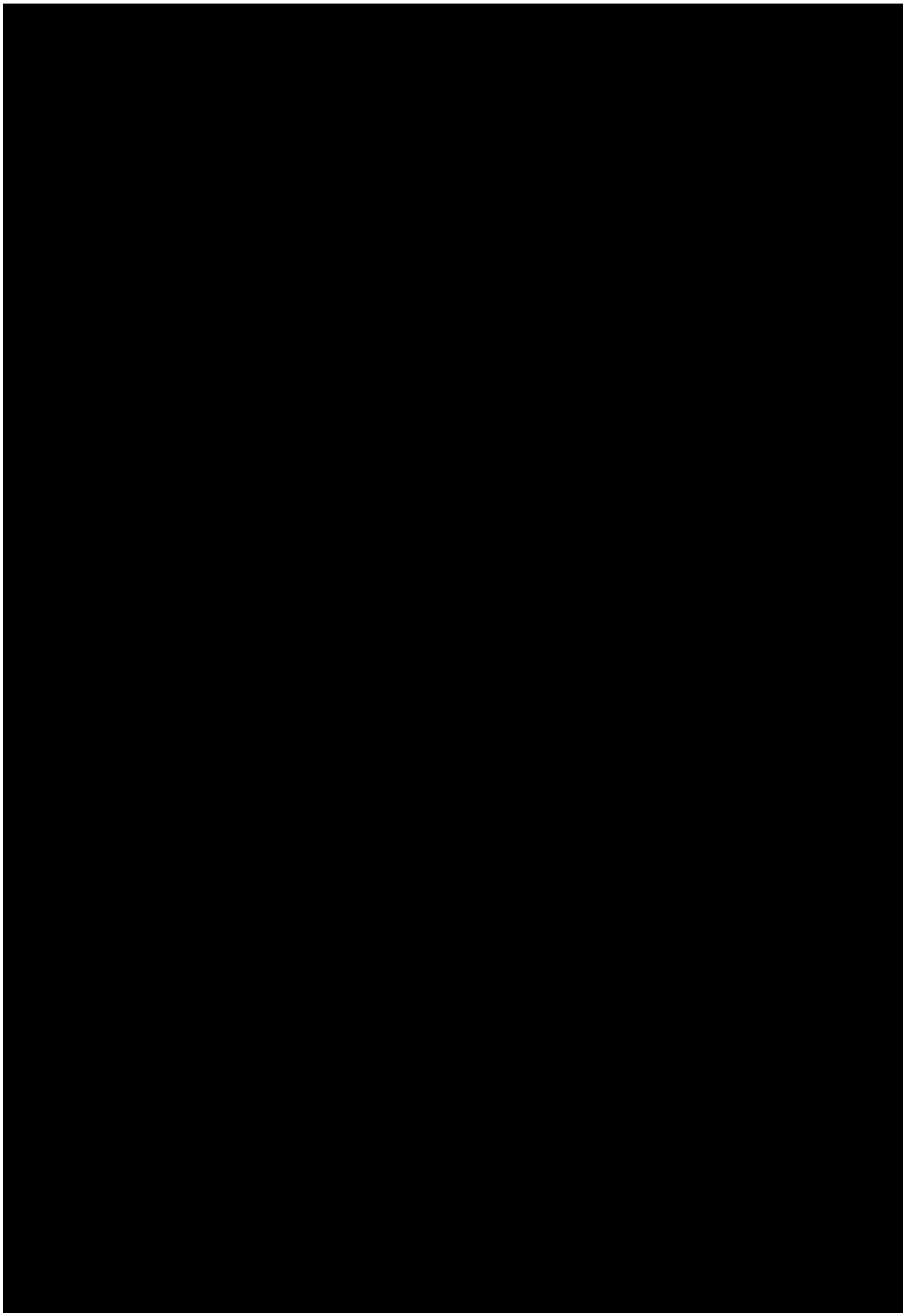
[redacted]

[redacted]

[redacted]

[redacted]

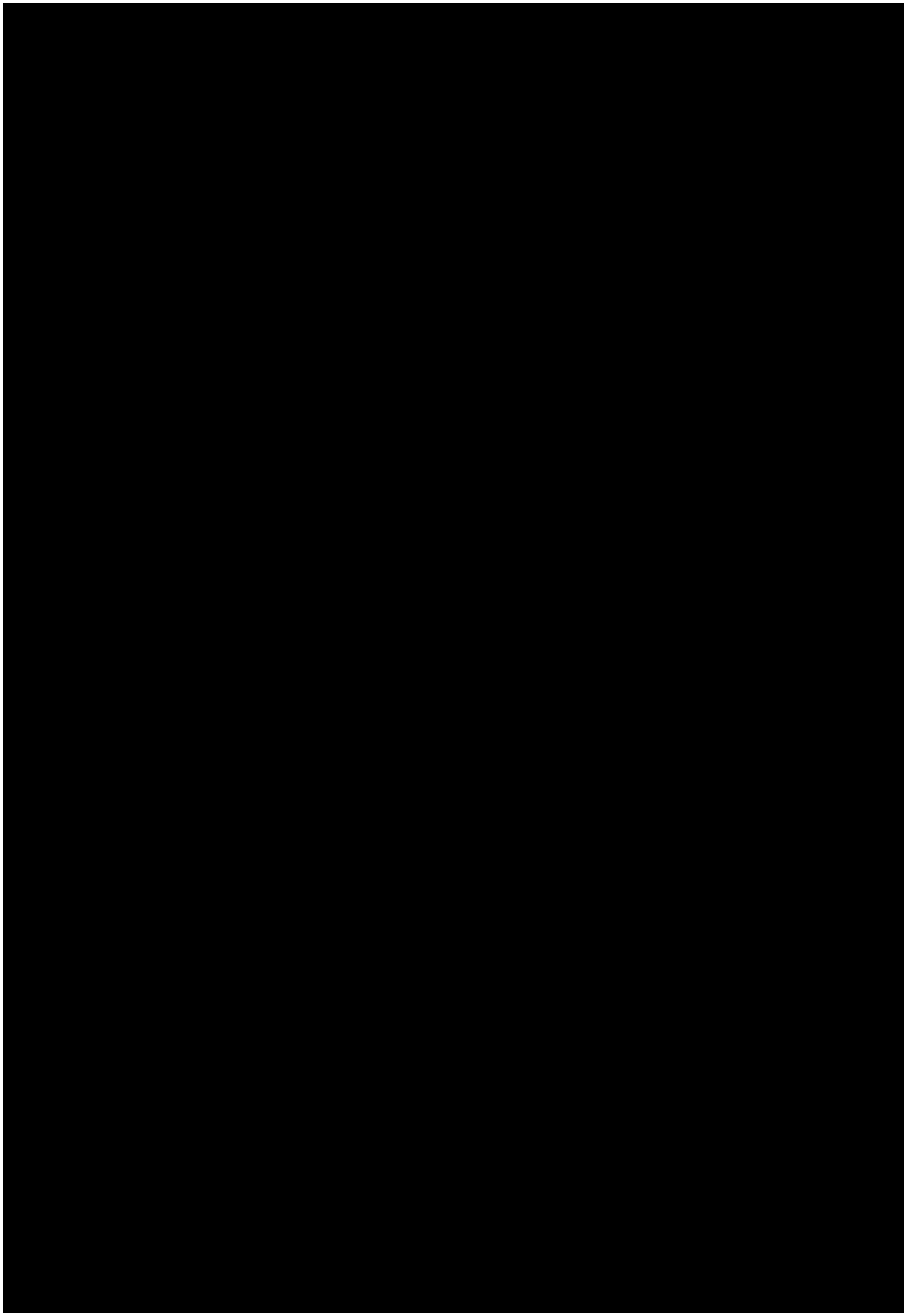
[redacted]



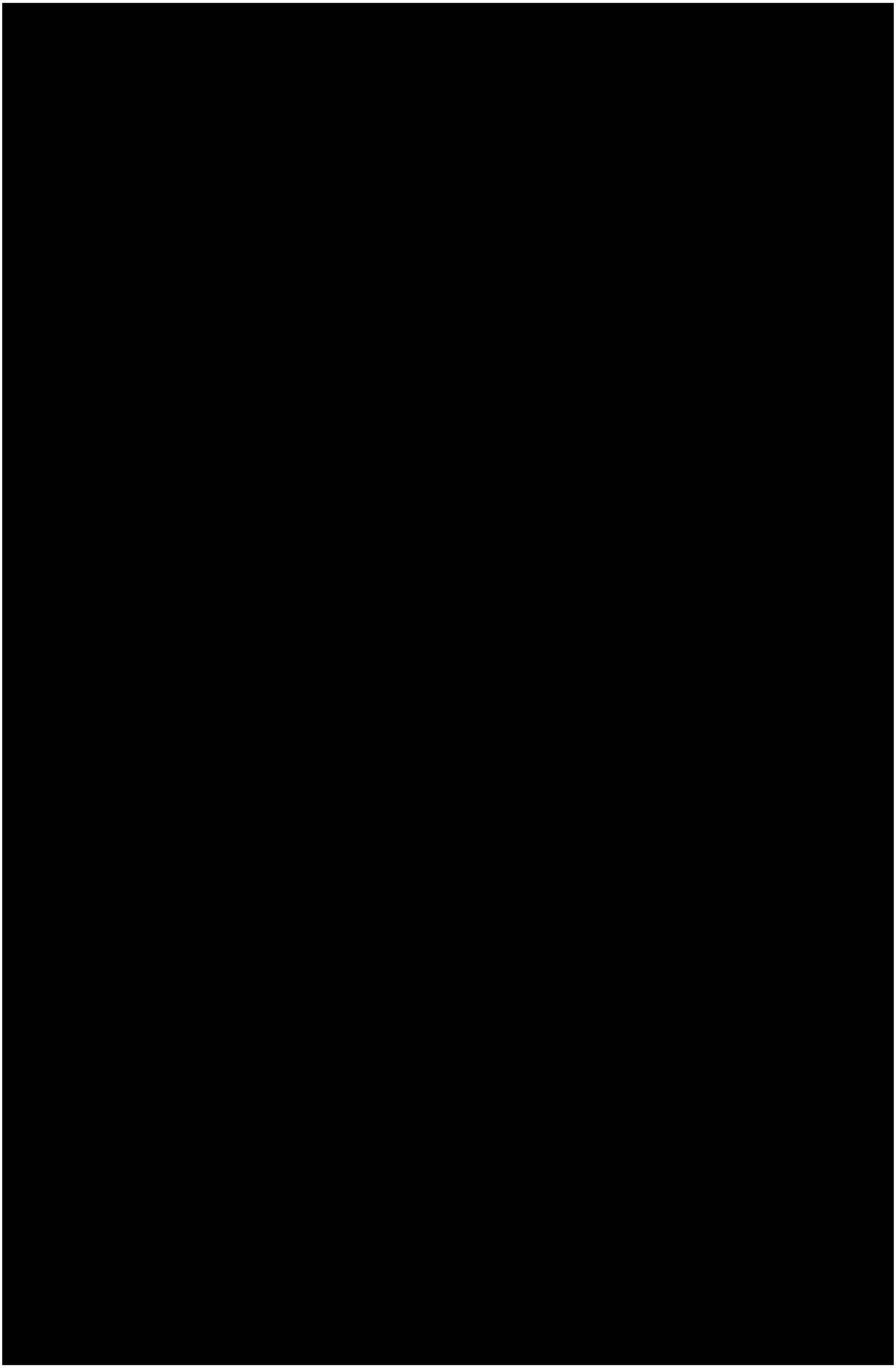
[redacted]

[redacted]

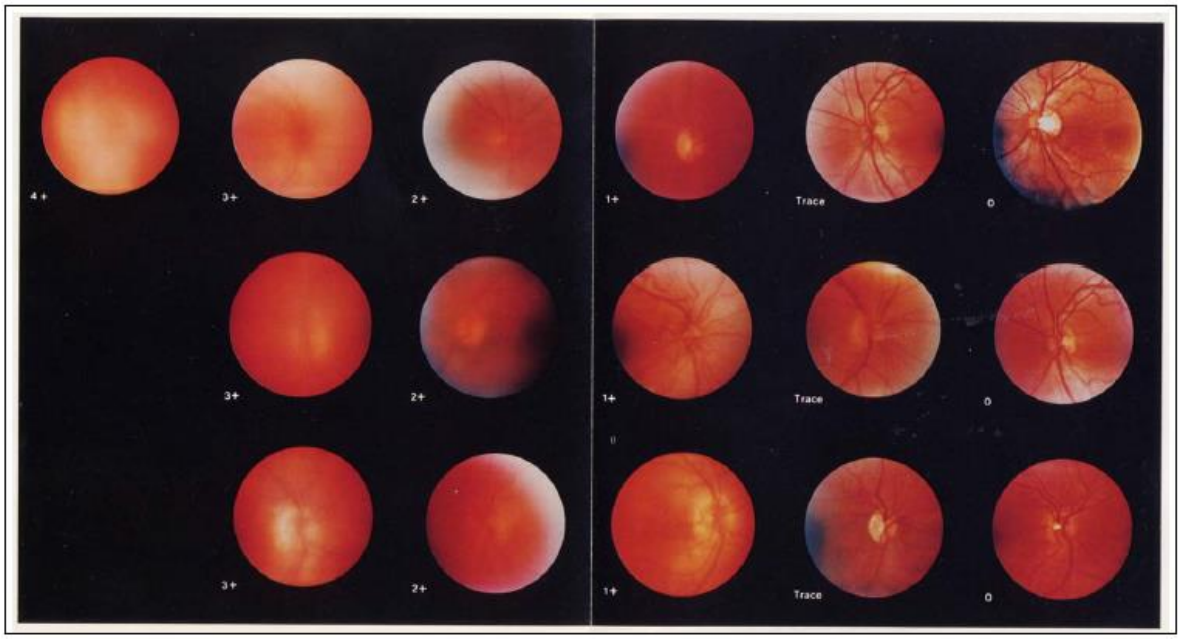
[redacted]



[redacted]



26.6. 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.