Official 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

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STATISTICAL ANALYSIS PLAN

Protocol Number: GT005-01 v9.0 (15 Dec 2022)

Name of Test Drug: GT005

Phase: I/II

Methodology: Open label, first in human

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

Sponsor Representative: [redacted]

Document Date: **17 June 2024**

Document Version: **04.00**

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Protocol:	GT005-01 (FOCUS)		
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SIGNATURE PAGE

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Sponsor:	Gyroscope Therapeutics Limited Rolling Stock Yard 188 York Way London N7 9AS United Kingdom
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[redacted] **Author:**
[redacted], **Ph.D.**
[redacted]

Signature: [redacted]
Email:

Signature:_____
Date: 17-Jun-2024

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

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Sponsor Signatory:
[redacted], PhD
Novartis Pharma AG
CH-4056 Basel

Signature:

Email: [redacted]

Signature:_____

Date: 17-Jun-2024

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DOCUMENT HISTORY

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
06-FEB-2023	*Prior to 1st IA DB lock*	*N/A*	*First version*	*NA*
28-JUN-2023	*Prior to 2nd IA DB lock*	*Sponsor Decision*	*Clarified unscheduled visit handling* *Removed post-baseline subgroup definitions for subgroup analysis, added correlation plot for GA area growth vs CFI level changes.* [redacted] *Defined representation of data for study cohorts with different cutoff dates (Week 96 for TVSI, Week 48 for SDS Orbit)*	*Section 3.1.1* *Section 3.7* [redacted] *Section 3.10*
24-NOV-2023	*Prior to final DB lock*	*Sponsor Decision*	*Removed subgroup analysis, corrected order of MMRM covariance matrices to be used.* *Added percentage of patients with full dose delivery for evaluation of successful delivery for Orbit SDS cohorts* [redacted]	*Section 3.7* *Section 3.7* [redacted]

[redacted]

LIST OF IN-TEXT TABLES

Table Page

ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
ACC	Reading accessibility index
AE	Adverse events
[redacted]	[redacted]
AMD	Age-related macular degeneration
BCEA	Bivariate contour ellipse area
BCVA	Best corrected visual acuity
CFI	Complement Factor I
CNV	Choroidal neovascularization
CPS	Critical print size
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
ETDRS	Early treatment for diabetic retinopathy
FAF	Fundus autofluorescence
FAS	Full Analysis Set
FIH	First in human
GA	Geographic atrophy (also known as macular atrophy)
hCFI	Human CFI
ICH	International Conference on Harmonisation
LLVA	Low luminance visual acuity
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RV	Rare variant
SAE	Serious adverse event
SAP	Statistical analysis plan

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Abbreviation	**Definition**
SD-OCT	Spectral domain optical coherence tomography
SDS	Subretinal Delivery System
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
[redacted]	[redacted]
WHO	World Health Organization

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling of the data collected in the clinical trial for Gyroscope Therapeutics with Protocol GT005-01: 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 (AMD). This SAP is based on the Clinical Study Protocol v 9.0, dated 15 December 2022.

The planned analyses identified in this SAP provide the basis for the results section of the clinical study reports and may be used in regulatory submissions or publications. Any differences in the planned analyses relative to the study protocol will be highlighted in the CSRs.

1.1. Study design

This is an open label first in human (FIH) Phase I/II multicenter study to evaluate the safety, dose response and efficacy of GT005 in subjects with geographic atrophy (GA) due to AMD. The study will be conducted in four parts and approximately 65 subjects will be enrolled.

Part 1 (dose-escalation) will test three dose cohorts ([redacted] vg), 3-5 subjects per cohort, with GT005 delivered via the transvitreal procedure.

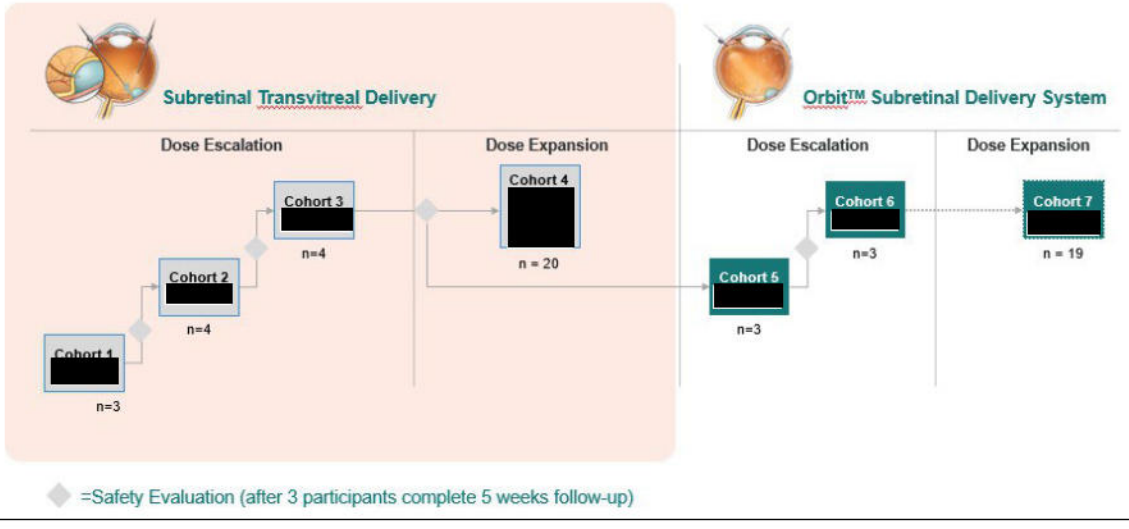
Part 2 (dose-expansion) will enroll up to 20 subjects in Cohort 4 with GT005 delivered via the transvitreal procedure.

Part 3 (dose-escalation and evaluation of two doses of GT005 delivered with the Orbit Subretinal Delivery System (SDS); subretinal delivery via a suprachoroidal cannulation) will enroll 3-5 subjects at the mid and high dose ([redacted] vg, Cohorts 5 and 6). Part 3 is independent of, and may be conducted in parallel to, Part 2.

Part 4 (dose-expansion) will enroll up to 20 subjects in Cohort 7 with GT005 delivered with the Orbit SDS.

The study will, for the individual subjects, consist of up to 14 visits over a 5-year period and will involve an independent Data Safety Monitoring Board (DSMB). For further details, refer to the GT005-01 Protocol.

Figure 1 Overview of the study design



1.2. Study objectives and endpoints

Study objectives and related endpoints are described in Table 1 below.

Table 1 Objectives and related endpoints

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 the 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]

2. SUBJECT POPULATIONS

2.1. Population definitions

The **All Enrolled Set** includes all patients who signed informed consent. This analysis set will be used to summarize patient disposition and for summaries of successful GT005 and BSS delivery rates of SDS orbit device.

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.

2.1.1. Subgroups of interest

Subgroup analyses will be performed for selected efficacy variables . The FAS can be stratified into two CFI variant subgroups: **CFI rare variant** subgroup of patients with rare variant resulting in CFI haploinsufficiency, and **Broad GA** subgroup including the rest of patients in the study; [redacted]

2.2. Protocol deviations

Protocol deviations will be identified and recorded by the study monitor in the Monitoring Visit Reports and/or the electronic data capture (EDC) system. Prior to locking the database for the analyses supporting clinical study reports, the relevant important protocol deviations will be identified. They will be classified as CSR non-reportable or CSR reportable based on their effect on the rights, safety, or wellbeing of the subjects and/or the quality and integrity of the data. CSR reportable protocol deviations will be summarized for SAF. The CSR reportable protocol deviations based on SAF will be provided in a listing.

No exclusions of patients from SAF and FAS will occur due to protocol deviations.

Alternative treatment for GA in the study eye during long-term follow up is not prohibited in the protocol but cannot be excluded. In this case efficacy and assay variables will be censored at last observation prior to the start of the alternative treatment. The censoring of data in such cases will be derived from concomitant medication data.

3. STATISTICAL METHODS

3.1. General information

Two interim analyses and a clinical study report (CSR) are planned. First interim analysis will include data up to Week 72 from cohorts 1-4 with GT005 delivered via the transvitreal procedure. Second interim analysis will include data from cohorts 1-4 up to Week 96 and from Orbit SDS administration cohorts 5-7 up to Week 48. Clinical study report will be based on the analysis of all variables specified in this SAP from all 7 cohorts on data over 96 weeks.

All outputs will be incorporated into Word files and PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, biomarker assay, and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the number of observations, mean, median, quartiles, standard deviation, standard error (SE), minimum and maximum values will be presented. Where appropriate, 95% confidence intervals (CIs) for point estimates of the mean or proportion will be provided. Data will be listed and summarized using descriptive statistics by dose, by route of administration, and by assessment visits as appropriate. Efficacy and biomarker assay data will additionally be summarized by CFI rare variant and broad GA subgroups. All ocular evaluations and ocular adverse events, where appropriate, will be presented by eye (Study Eye, Fellow Eye).

No formal statistical hypothesis testing will be performed for this study.

Medical history, concurrent procedures and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Reference List dictionary version Mar 2020.

All statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted.

3.1.1. Study days and visit windows

Study day is defined as the number of days relative to the date of the subretinal injection with the study drug. For a particular date, study day will be calculated as follows:

- for dates on or after the date of study treatment: Study day = Assessment date – Date of treatment administration + 1;
- for dates prior to the date of administration of study treatment: Study day = Assessment date – Date of treatment administration.

Baseline values are defined as values from the last assessment prior to surgery for the study treatment administration. All data collected after the treatment administration are defined as post-baseline.

The end of study date is the date when a patient completes or discontinues the study. For reporting data by visit in outputs, the end of study visit will be allocated to the actual (reported) visit number. If the end of study date is not on a scheduled visit, then the end of study visit will be allocated, based on study day, to the closest future scheduled study visit.

For scheduled visits, the analysis visits will be the actual (reported) visits.

Data collected at unscheduled visits will not be used in 'by-visit' tabulations or graphs but will be included in analyses based on all post-baseline values such averages over a given period or summaries of maximum/minimum values. These unscheduled visits data will not be used in analyses with mixed model for repeated measures (MMRM). All data collected at unscheduled visits will be included in the listings.

3.2. **Missing data**

There will be no imputation of missing data performed except for GA area growth analysis, which will be based on MMRM model and thus missing data will be implicitly imputed assuming Missing at Random (MAR). All data recorded on the CRF will be included in data listings that will accompany the clinical study report. Missing adverse event (AE) dates are imputed as follows:

- If AE end year is missing, or AE is ongoing, the end date will not be imputed.
- If AE end month is missing, then AE end date = min(31 Dec of AE end year, date of study discontinuation/completion).
- If the AE end day is missing, then AE end date = min(Last day of the AE end month, date of study discontinuation/completion).
- If AE start year is missing and AE end date < TRT date, then AE start date = earliest visit date
- If AE start year is missing and AE end date => TRT date or ongoing, then AE start date = TRT date
- If both AE start and end dates are missing and AE is not ongoing, both dates are set to TRT date.
- If AE start year < TRT year or AE start year > TRT year, and
    - month is missing, then AE start date = 01 Jan of AE start year
    - day is missing, then AE start date = 01 of AE start month-year
- If AE start year = TRT year, and
    - month is missing and AE end date < TRT date, then AE start date = 01 Jan AE start year
    - month is missing and AE end date => TRT date or ongoing, then AE start date = TRT date
    - month < TRT month or month > TRT month, then AE start date = 01 of AE start month-year
    - month = TRT month, then AE start date = min(TRT date, AE end date)

The same algorithm will be applied to impute start and end of concomitant medication.

The imputed dates will only be used to classify events, medications, or procedures as treatment emergent, concomitant or concurrent . Imputed dates will only be used in the table analyses. Listings will display the available date data. Missing dates in medical history will not be imputed except the date of initial diagnosis of GA which will apply the same date imputation algorithm mentioned above.

3.3. **Sample size justification**

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

3.4. Subject disposition

The following summaries will be included in the disposition table considering all enrolled patients: number and percent of patients who are enrolled into the study, failed screening, treated, discontinued the study prior to or at the study week of the analysis (including reasons for discontinuation) by treatment dose, route of administration and overall.

A listing of patients who discontinue from the study prior to the end of study will be provided by treatment dose and route of administration. The listing will identify date, study day and the reason of study discontinuation.

Patients who sign an informed consent form and who are subsequently found to be ineligible prior to study treatment will be considered a screen failure. Screen failure information will not be summarized but only listed.

Number and percent of enrolled patients who were excluded (i.e., not evaluable) from SAF or FAS will be presented. A listing of patients and the reason of exclusion from corresponding analysis set will also be presented.

3.5. Demographic and baseline characteristics

Demographics and baseline ocular characteristics for the study eye will be summarized with descriptive statistics for the FAS by dose, route of administration and overall. Demographic characteristics will include age, gender, race, ethnicity and CFI rare variant subgroup. Baseline ocular characteristics for the study eye will be additionally summarized by CFI variant subgroups per route of administration. Ocular baseline characteristics include:

- Study eye selection (left eye OS or right eye OD)
- Best corrected visual acuity BCVA (in ETDRS letters)
- Low-luminance visual acuity LLVA (in ETDRS letters)
- Low-luminance deficit (BCVA-LLVA, in ETDRS letters)
- GA lesion area (mm2) as assessed by FAF
- GA contour (Unifocal, Multifocal) as assessed by FAF
- GA foveal involvement (Foveal, Extrafoveal) as assessed by FAF and OCT
- Junctional zone pattern (Atypical, Banded, Diffuse, Focal, Cannot Grade) as assessed by FAF
- Drusen area (mm2) as assessed by CFP
- Presence of hard drusen (Yes, No, Cannot Grade) as assessed by CFP
- Maximum drusen size within ETDRS Grid (Large, Intermediate, Small, Cannot Grade) as assessed by CFP
- Presence of reticular pseudodrusen (Yes, No, Cannot Grade) as assessed by OCT
- Presence of soft drusen (Yes, No, Cannot Grade) as assessed by CFP
- Presence of calcified drusen (Yes, No) as assessed by CFP

- Presence of cuticular drusen (Yes, No) as assessed by CFP
- CSFT (µm) as assessed by OCT
- Years since GA diagnosis

3.6. Medical history

Medical history and current medical conditions for SAF will be listed for ocular (both study eye and fellow eye) and non-ocular events. No summary table will be produced.

3.7. Efficacy analyses

Efficacy analyses will be conducted using the FAS by treatment dose and route of administration.

GA area (mm2) change from baseline in the study eye as assessed by FAF will be presented in spaghetti plots and in a summary by visit table. It will also be summarized in a table and line plots as least-squares means with 95% CI by visit using MMRM model with fixed effects for treatment (defined as dose and route of administration), study visit, baseline GA area (mm2), treatment by visit interaction and visit by baseline GA area interaction.

Square root of GA area (mm) change from baseline in the study eye will be presented in spaghetti plots and in a summary by visit table. It will also be summarized in a table and line plots as least-squares means with 95% CI by visit using MMRM model with fixed effects for treatment, study visit, square root of baseline GA area (mm), treatment by visit interaction and visit by square root of baseline GA area (mm) interaction. MMRM analysis will be repeated for CFI rare variant subgroups and [redacted] by replacing in the model treatment with subgroups of interest.

[redacted]

For MMRM analysis an unstructured covariance matrix will be used to model the within-patient error. If an MMRM model with an unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached:, first-order autoregressive , Toeplitz , compound symmetry and variance components.
Additionally, scatter plots with linear trend lines for square root of GA area size (mm) change from baseline at the target analysis visit vs. last observed CFI levels before the target analysis visit in the vitreous and aqueous samples will be generated by treatment groups.

[redacted]

[redacted]

The following **macular sensitivity parameters by Mesopic Microperimetry** will be summarized by visit:

- Fixation stability measured with bivariate contour ellipse area (BCEA) at 63% and 95% proportional values (Deg^2)
- Mean sensitivity (dB)
- Number of scotomatous points
- Percentage of fixation loss

[redacted]

[redacted]

The rate of successful delivery of full dose GT005 to the subretinal space for patients treated using the Orbit Subretinal Delivery System (cohorts 5-7) will be reported as number of full doses delivered divided by number of Orbit SDS devices used. **Rate of successful balanced salt solution** (BSS/BSS+) delivered will be reported as number of BSS/BSS+ administrations divided by number of devices used. Additionally, percentage of patients with full dose of GT005 delivered among patients intended to be treated using SDS Orbit will be reported. Listing of failed deliveries of GT005 or balanced salt solution (BSS/BSS+) will be provided along with the reasons for delivery failures.

All efficacy endpoints will be provided in data listings for FAS. [redacted]

3.8. **Biomarkers and [redacted] analyses**

Levels of complement factors in aqueous, vitreous and plasma samples will be graphically presented using geometric means and 95% CI over time (visit) by treatment administration route and, separately, by CFI subgroups (CFI rare variant and broad GA). Concentration values above upper limit of quantification (ULOQ) will be set ULOQ, values below lower limit of detection (LOD) will be set to LOD using **Table 4**.

Box plots of fold change from baseline for CFI levels at last sampling visit for the analysis period, separately for aqueous and vitreous samples, vs.:

- Treatment dose and route of administration
- CFI variant subgroup (CFI rare variant, Broad GA)
- [redacted]

will be presented.

[redacted]

A summary of data outside of quantification limits by visit will be presented.

[redacted]

3.9. Safety Analyses

3.9.1. Adverse events

Analyses of adverse events will be performed in the SAF for treatment-emergent adverse events (TEAE). TEAEs are adverse events that are first identified or worsened after receiving the study treatment. Only treatment-emergent adverse events will be presented in the summary tables. Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). The number (and proportion) of patients with TEAEs will be summarized by treatment dose and administration route at each analysis timepoint according to Table 5**.** AEs occurred after surgery for treatment administration and before deferred GT005 administration will be listed and included in footnotes of relevant TEAE summary tables.

Table 5 TEAE summaries by treatment dose per administration route (if applicable)

TEAE summary	**AE categories**		
	Ocular AE in the study eye	**Ocular AE in the fellow eye**	**Non- ocular AE**
All AEs by primary SOC and PT	Y	Y	Y
All AEs by maximum severity	Y	Y	Y
AEs related to study treatment by SOC and PT	Y		Y
AEs related to surgical procedure by SOC and PT	Y		Y
AEs related to Orbit SDS procedure by SOC and PT	Y		Y
SAEs by SOC and PT	Y	Y	Y
SAEs related to study treatment by SOC and PT	Y		Y
SAEs related to surgical procedure by SOC and PT	Y		Y
SAEs related to Orbit SDS procedure by SOC and PT	Y		Y

[redacted]

All adverse events occurring in the study will be listed in subject data listings. By-subject listings will also be provided for the following: subject deaths; serious adverse events; [redacted]

3.9.2. Visual Acuity (BCVA and LLVA)

Best corrected visual acuity (BCVA), low-luminance visual acuity (LLVA) and low-luminance deficit (LLD) scores via the ETDRS Chart will be summarized as actual and change from baseline values over time (visit) by eye,

treatment dose, and route of administration. Plots for mean changes from baseline for BCVA, LLVA and LLD (with 95% CI) over time will be presented.

All BCVA, LLVA and LLD assessments will be provided in data listings.

3.9.3. **Laboratory Data**

Laboratory parameters listed in Table 6 will be presented graphically using boxplots of absolute change from baseline values by treatment dose and route administration and by visit. No summary by visit tables will be provided.

A summary table with counts and percentage of patients satisfying the criteria representing clinically relevant abnormalities defined in Table 6 at any visit will be presented. A listing for patients satisfying at least one criterion in Table 6 at any visit will also be presented.

Table 6 Clinically notable laboratory values

Test	Critically Low	Critically High	Units
Hemoglobin	< 7.0	> 20.0	g/dL
White Cell Count	< 2.0	> 35.0	x10E3/uL
Platelets	< 50	> 1000	x10E3/uL
Glucose	< 40	> 500	mg/dL
Calcium	< 6.0	> 12.0	mg/dL
Phosphate	< 0.9		mg/dL
Sodium	< 120	> 160	mmol/L
Potassium	< 3.0	> 6.0	mmol/L
Magnesium	<0.74	> 1.0	mmol/L
AST		41	U/L
ALT		45	U/L
Total bilirubin		21	umol/L

3.9.4. **Vital Signs**

A summary table with counts and percentage of patients satisfying the criteria given in Table 7 at least at one visit will be presented. A listing for patients satisfying at least one criterion in Table 7 will also be presented.

A line plot of mean change from baseline in the vital sign parameters listed in Table 7 by study visit and by treatment dose and route administration with error bars representing 95% CI will be presented. The x-axis will be study visit and the y-axis will be the mean change from baseline value.

Table 7 Clinically notable vital signs

Variable	Category	Critical values
Systolic blood pressure (mmHg)	High	Either >180 with an increase from baseline >30 or >200 absolute
	Low	Either <90 with a decrease from baseline >30 or <75 absolute
Diastolic blood pressure (mmHg)	High	Either >105 with an increase from baseline >20 or >115 absolute
	Low	Either <50 with a decrease from baseline > 20 or <40 absolute

Pulse rate (bpm)	High	Either >120 with an increase from baseline of >25 or > 130 absolute
	Low	Either <50 with a decrease from baseline >30 or <40 absolute

[redacted]

3.10. **Interim analyses**

Interim analyses will present patient disposition, demographic and baseline characteristics and present analysis of selected safety, efficacy and assay variables using methods outlined in the corresponding sections. A reduced number of variables will be reported in the interim analyses.

Ocular baseline characteristics in the study eye will include:

- Study eye selection (left eye OS or right eye OD)
- Best corrected visual acuity BCVA (in ETDRS letters)
- Low-luminance visual acuity LLVA (in ETDRS letters)

- Low-luminance deficit (BCVA-LLVA, in ETDRS letters)
- GA lesion area (mm2) as assessed by FAF
- GA contour (Unifocal, Multifocal) as assessed by FAF
- GA foveal involvement (Foveal, Extrafoveal) as assessed by FAF and OCT
- Junctional zone pattern (Atypical, Banded, Diffuse, Focal, Cannot Grade) as assessed by FAF
- [redacted]
- Years since GA diagnosis

Analysis of GA area size (mm2) and square root of GA area size (mm) in the study eye.

Scatter plots with linear trend lines for square root of GA area size (mm) change from baseline at the target analysis visit vs. last observed CFI levels before the target analysis visit in the vitreous and aqueous samples by treatment groups.

Treatment-emergent adverse events summary tables

- Ocular and non-ocular TEAEs by System Organ Class and Preferred Term
- [redacted]

BCVA: mean BCVA change from baseline plot in study eye by treatment dose.

[redacted]

- [redacted]
- [redacted]

The interim reports with Orbit SDS administration cohorts will include the rate of successful full dose delivery of GT005 to the subretinal space and the rate of successful delivery of balanced salt solution (BSS) or BSS PLUS to the subretinal space.

For interim analyses with cutoff visits different between transvitreal and Orbit SDS cohorts, the safety summary tables will be presented for all cohorts up to last common visit (i.e., Week 48 for second interim analysis) and separately for transvitreal administration cohorts up to later cutoff visit (i.e., Week 96 for second interim analyses).

3.11. **Prior and concomitant therapies**

Prior therapies (medications, non-drug therapies and procedures) are defined as therapies completed prior to the study treatment. Concomitant therapies are those received after the start of study treatment including those already started prior to the start of the study treatment.

Prior and concomitant medications will be coded according to the WHO Drug Reference List dictionary,

with maximum coded Anatomical Therapeutic Classification (ATC) level and preferred term.

Prior and concomitant medications, non-drug therapies and procedures will be listed for each treatment dose and administration.

There are no prohibited concomitant medications/procedures for this study, no summary table will be produced.

4. CHANGES TO PLANNED ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan.

5. REFERENCES

Calabrèse, Aurélie, et al. "Development of a reading accessibility index using the MNREAD acuity chart." JAMA ophthalmology 134.4 (2016): 398-405.

Varma, Rohit, et al. "Maximum reading speed in patients with geographic atrophy secondary to age-related macular degeneration." Investigative Ophthalmology & Visual Science 59.4 (2018): AMD195-AMD201.

Gyroscope FOCUS Statistical Analysis Plan v04.00 17Jun2024

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"Gyroscope FOCUS Statistical Analysis Plan v04.00 17Jun2024" History

Document created by [redacted]
2024-06-17 - 12:23:05 PM GMT-[redacted]

Document emailed to [redacted] for signature
2024-06-17 - 12:25:17 PM GMT

Document emailed to [redacted] for signature
2024-06-17 - 12:25:17 PM GMT

[redacted] authenticated with Adobe Acrobat Sign.
2024-06-17 - 12:26:10 PM GMT

Document e-signed by [redacted]
Signing reason: Approve
Signature Date: 2024-06-17 - 12:26:11 PM GMT - Time Source: server-[redacted]

Email viewed by [redacted]
2024-06-17 - 12:31:30 PM GMT-[redacted]

[redacted] authenticated with phone by verifying one-time code sent to the phone number [redacted]
Challenge: The user opened the agreement.
2024-06-17 - 12:31:52 PM GMT

Signer [redacted] entered name at signing as [redacted]
2024-06-17 - 12:35:12 PM GMT-[redacted]

[redacted] authenticated with phone by verifying one-time code sent to the [redacted]

Challenge: The user completed the signing ceremony.

2024-06-17 - 12:35:12 PM GMT

Document e-signed by [redacted]

Signing reason: Approve

Signature Date: 2024-06-17 - 12:35:14 PM GMT - Time Source: server-[redacted]

Agreement completed.

2024-06-17 - 12:35:14 PM GMT