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Clinical Development

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EXPLORE: A Phase 2, Outcomes Assessor-Masked, Multicenter, Randomized Study to Evaluate the Safety and Efficacy of Two Doses of GT005 Administered as A Single Subretinal Injection in Subjects With Geographic Atrophy Secondary to Age-Related Macular Degeneration

Statistical Analysis Plan (SAP)

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[redacted]				

Table of contents

List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Events of Special Interest
AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CFI	Complement factor I
CFP	Color Fundus Photography
CI	Confidence Interval
CNV	Choroidal neovascularisation
CRO	Contract Research Organization
CSFT	Central Sub Field Thickness
CSR	Clinical Study Report
DBL	Database Lock
ETDRS	Early Treatment for Diabetic Retinopathy
FAF	Fundus autofluorescence
FAS	Full Analysis Set
FRI	Functional Reading Independence
GA	Geographic atrophy
IRT	Interactive Response Technology
LLD	Low Luminance Difference
LLVA	Low-luminance Visual Acuity
LSM	Least-Squares Mean
MAR	Missing at Random
MMRM	mixed model repeated measures
MNRead	Minnesota low-vision Reading test
OCT	Optical Coherence Tomography
PD	Protocol Deviation
PT	Preferred Term
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TAb	Total (or binding) Antibodies
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
VFQ-25	Visual Function Questionnaire-25

1 Introduction

The EXPLORE study (CPPY988A12202) is being terminated early as Novartis has made the decision to stop the current clinical development program for GT005 in subjects with geographic atrophy based on the results from the futility interim analysis. All GT005-treated subjects will be transferred into the long-term safety follow-up study, ORACLE (CPPY988A12203B).

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in/changed from the study protocol, and to provide detailed statistical methods that will be used for the EXPLORE Clinical Study Report (CSR).

A final analysis will be conducted once all enrolled subjects complete (or discontinue prior to) the Week 96 visit and final Database Lock (DBL) is achieved. Data will be analyzed according to the data analysis plan described in this document that will be incorporated into the CSR.

This SAP is based on the EXPLORE Clinical Study Protocol V6.0, dated 6 December 2022.

1.1 Study design

This is a Phase 2, outcomes assessor-masked, multicenter, randomized study to evaluate the safety and efficacy of two doses of GT005 administered as a single-time subretinal injection in subjects with geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Approximately 202 subjects are planned to be randomized to GT005 or the untreated control group. Subjects who are screened, but not randomized, will be classed as Screen Failures and will be replaced.

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

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

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

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

Randomization/Stratification

Subjects in Part 1 will be randomized to one of two dose groups: low dose (vg) or high dose (vg). Subjects in Part 2 will be randomized to one of two treatment groups: low dose (vg) or untreated control.

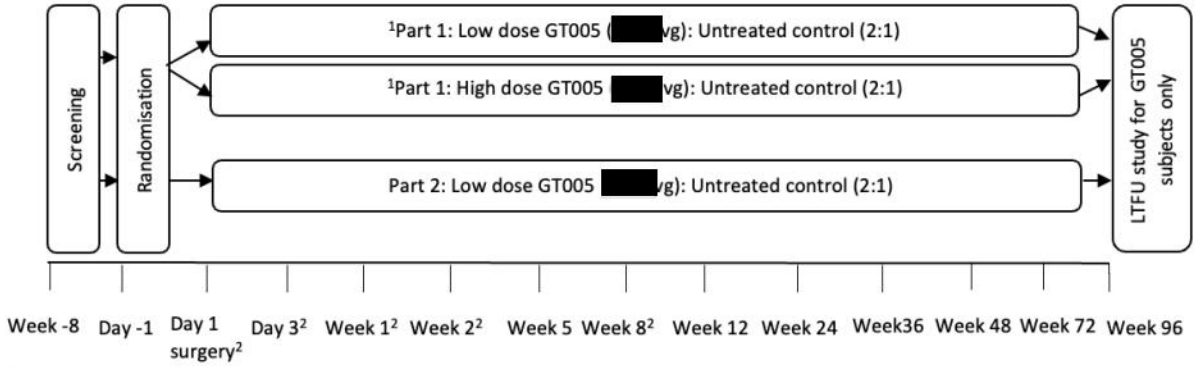
A permuted-block randomization method will be used to obtain an approximately 2:1 ratio between treatment with GT005 and the untreated control group(s) for each dose group within each stratum (Figure 1-1).

A treatment assignment will be allocated by Interactive Response Technology (IRT) (additional details will be found in the IRT reference manual provided to each site). Authorized personnel at investigative sites will use the IRT system to randomize subjects. IRT will assign subjects to a treatment code number based on a pre-defined randomization list that will be created by a statistician who is independent from the study.

Upon randomization, subjects will be immediately informed of allocation.

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

Figure 1-1 Study Design



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

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

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD	• The change from baseline to Week 48 in GA area as measured by fundus autofluorescence (FAF)
Secondary	
• To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD	• The change from baseline through Week 96 in GA area as measured by FAF
• To evaluate the safety and tolerability of GT005	• Frequency of treatment emergent adverse events (TEAE) through Week 96
• To evaluate the effect of GT005 on retinal anatomical measures	• Change in retinal morphology on multimodal imaging through Week 96
• To evaluate the effect of GT005 on functional measures	• Change in best corrected visual acuity (BCVA) Score via the early treatment for diabetic retinopathy (ETDRS) chart through Week 96

	• Change in low luminance difference (LLD) via the ETDRS chart through Week 96
• To evaluate the effect of GT005 on visual function	• Change in reading performance as assessed by Minnesota low-vision reading test (MNRead) chart through Week 96 • Change in functional reading independence (FRI) index through Week 96
• To evaluate the effect of GT005 on patient-reported outcomes	• Change in quality of life measured on the visual function questionnaire-25 (VFQ-25) through Week 96

1.2.1 Primary estimand(s)

The primary estimand will focus on the effect attributable to different doses of GT005 on GA change on FAF at Week 48 in subjects who have not received alternative GA medications or therapies in the study eye.

The primary estimand is described by the following attributes:

1. **Population:** Subjects with GA secondary to AMD. Details on the target population are defined by the study inclusion and exclusion criteria.
2. **Variable:** Change from baseline in GA lesion size (mm^2) based on FAF at Week 48
3. **Treatment:** The randomized treatment (different doses) of the investigational therapy GT005 delivered through transvitreal subretinal injection.
4. **Summary Measure:** The treatment difference of the variable means between GT005 and untreated control, represented as % relative to untreated control.
5. **Intercurrent events and data handling strategy:** defined in Table 1-2.

Table 1-2 Intercurrent Events and Corresponding Primary Data Handling Strategies

Intercurrent event	Data handling strategy
Subject receives alternative GA medications or therapies in the study eye	GA lesion size data collected in the study eye after the subject initiates alternative GA medications or therapies will be censored and imputed assuming missing at random (MAR)

2 Statistical methods

2.1 Data analysis general information

The analyses will be performed by the Contract Research Organization (CRO) using SAS 9.4.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. These summary statistics will be presented by the treatment group unless otherwise specified. Where appropriate, point estimates and confidence intervals (CI) of treatment group differences will be provided.

2.1.1 General definitions

2.1.1.1 Study treatment

The following treatment groups will be presented:

- Untreated control
- Low dose GT005 ([redacted] vg)
- High dose GT005 ([redacted] vg)

2.1.1.2 Baseline and post-Baseline

Baseline (Day 1) is defined as

- the day following randomization for subjects randomized to untreated control
- the day of successfully receiving GT005 administration for subjects randomized to GT005
- or the latest surgery date for subjects who were randomized to GT005 but failed to receive GT005 administration on the first attempt to surgery (if applicable)

The baseline value for efficacy and safety variables is the last available value (scheduled or unscheduled) collected prior to the date of *Baseline*, or on the date of *Baseline* but prior to the time of GT005 administration for GT005 treatment groups.

All data collected after the date of *Baseline* are defined as post-baseline. The *study day* for a baseline or post-baseline scheduled or unscheduled visit is defined as:

$$Study\ day = \begin{cases} (\text{Date of visit}) - (\text{Date of randomization}) & \text{Untreated} \\ (\text{Date of visit}) - (\text{Date of treatment administration}) + 1 & \text{GT005} \end{cases}$$

The *study day* for a scheduled or unscheduled visit before baseline is defined as

$$Study\ day = \begin{cases} (\text{Date of visit}) - (\text{Date of randomization}) - 1 & \text{Untreated} \\ (\text{Date of visit}) - (\text{Date of treatment administration}) & \text{GT005} \end{cases}$$

2.1.1.3 End of study mapping

The end of study date is the date when a subject 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.

2.1.1.4 Unscheduled visits

For unscheduled visits, the analysis visits will be derived with windowing where appropriate (e.g., Visit 3 ± 3 days) as per the protocol. For scheduled visits, the analysis visits will be the actual (reported) visit number.

Data collected at unscheduled visits will not be used in 'by-visit' tabulations, graphs or analyses unless it can be mapped to a missed scheduled visit with the window specified per the protocol. If multiple unscheduled visits are allocated to the same missed scheduled visit:

- The unscheduled visit closest to the missed scheduled visit will be used
- If there are multiple unscheduled visits with the same distance to the missed scheduled visit, the latest one will be used

For analyses showing abnormalities, data from unscheduled visits will be considered individually, without mapping to a main visit.

For analyses based on all post-baseline values such as averages over a given period summaries of maximum/minimum values, data collected at unscheduled visits will be included.

All data collected at unscheduled visits will be listed.

2.1.1.5 Missing baseline and post-baseline data

Missing baseline data will not be imputed.

Observations with values ‘not done’, ‘not evaluable’, ‘not applicable’ will be treated as missing values.

In case of multiple entries for the same assessment are observed within one visit, the latest assessment value will be used.

2.1.1.6 Alternative GA medications or therapies

Avacincaptad pegol (Izervay) and pegcetacoplan (Syfovre) via intravitreal injection are Food and Drug Administration approved treatments for GA and are permittable alternative GA treatments in this study.

2.2 Analysis sets

The **All-Enrolled Set** includes all patients who signed informed consent. This analysis set will be used to summarize subject disposition.

The **Full Analysis Set (FAS)** will include all subjects who are randomized to GT005 or untreated control. The FAS will be used for the analysis of efficacy and safety data.

The number and percentage of subjects within each of the above analysis sets will be summarized.

2.2.1 Subgroup of interest

Not Applicable.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

Subject disposition will be summarized separately by treatment group and in total for the All-Enrolled Set: the number and percentage of screen failures (including the primary reason for screen failure), subjects enrolled, randomized, randomized and treated with GT005, completed study, discontinued the study prematurely (including the primary reason for premature study discontinuation).

A listing of subjects who discontinued study earlier than the planned end-of-study will be provided by treatment group for the FAS. This listing will identify the last visit completed and when the study was discontinued including the primary reason.

In addition, protocol deviations (PDs) will be listed and summarized by the number and percentage of subjects with each deviation category for the FAS.

2.3.2 Demographics and other baseline characteristics

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

Summary statistics will be presented for the study eye if they are baseline ocular characteristics. Listings for demographic and ocular baseline characteristics will be provided.

Baseline ocular characteristics for the study eye will be summarized by treatment group and in total for the FAS. 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 (LLD) (BCVA - LLVA in ETDRS letters)
- GA lesion area (mm^2) as assessed by FAF
- GA contour (Unifocal, Multifocal, Cannot Grade) as assessed by FAF
- GA foveal involvement (Foveal, Non-foveal, Cannot Grade) as assessed by FAF and optical coherence tomography (OCT)
- Junctional zone pattern (Atypical, Banded, Diffuse, Focal, Cannot Grade) as assessed by FAF
- Presence of hard drusen (Yes, No, Cannot Grade) as assessed by color fundus photography (CFP)
- Presence of soft drusen (Yes, No, Cannot Grade) as assessed by CFP
- Presence of calcified drusen (Yes, No, Cannot Grade) as assessed by CFP
- Presence of cuticular drusen (Yes, No, Cannot Grade) as assessed by CFP
- Presence of subretinal hemorrhage (Yes, No, Cannot Grade) as assessed by CFP
- Presence of intraretinal hemorrhage (Yes, No, Cannot Grade) as assessed by CFP
- Presence of reticular pseudodrusen (Yes, No, Cannot Grade) as assessed by OCT
- Central Subfield Thickness (CSFT) (µm) as assessed by OCT
- Years since GA diagnosis

2.3.3 Medical history

Medical histories/current medical conditions will be listed by treatment arm, including the reported term/PT/SOC, laterality if applicable, start/end date, ongoing status (Yes, No) indicating whether the event is ongoing by the time of analysis, etc. These outputs will be based on the FAS.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment

The FAS will be used for the analyses below.

GT005 is administered as a single-time subretinal injection into the study eye of subjects allocated to one of the two GT005 doses. The surgical procedure for subretinal administration of GT005 is based on a standardized methodology. It is conducted by an appropriately qualified Vitreoretinal Surgeon in an operating room under appropriate anesthesia. Subjects allocated to the untreated control will not receive any treatment.

Study treatment will be summarized by the number and percentage of subjects randomized, subjects underwent study surgery, subjects treated with GT005, subjects who did not complete the study surgery successfully (including the primary reason for preventing successful completion of surgery, related/unrelated to the surgery procedure). The number and percentage of subjects discontinued study prior to surgery (including the primary reason for discontinuation) will also be provided.

A listing for surgical and dose administration records will be provided.

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as drugs taken and stopped prior to the date of randomization. Any medication given at least once between the date of randomization and the last study visit will be a concomitant medication, including those that were started pre-baseline visits and continued into the treatment period. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of taking the medication.

Prior and concomitant medications will be coded according to the WHO Drug Reference List dictionary with Anatomical Therapeutic Classification (ACT) class and preferred term (PT).

Concurrent procedures will be summarized by treatment group and in total for ocular (study eye and fellow eye) and non-ocular events, presented with the number and percentage of patients by System Organ Class (SOC) and PT.

Prior medications and concomitant medications will be listed by treatment arms, including the reported name of medication/standardized medication name, indication, route of administration, laterality if applicable, start/end date, etc.

2.5 Analysis supporting primary objective(s)

The primary objective of this study is to evaluate the effect of GT005 vs untreated control on the progression of GA in subjects with GA due to AMD. This will be evaluated by measuring the GA area over time using FAF.

2.5.1 Primary endpoint(s)

The primary endpoint is the change from baseline to Week 48 in GA area as measured by FAF.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary endpoint will be estimated among treatment groups via least-squares means from a mixed model repeated measures (MMRM) analysis. The model will include the change from baseline in GA area measured by FAF as the dependent variable, GA area at the baseline as the covariate, assessment visit, treatment group, three interaction terms (assessment visit and treatment group, assessment visit and GA area at the baseline, GA area at the baseline and treatment group) as the fixed effect and subject as a random effect.

An unstructured within subject correlation structure will be used for the covariance matrix. If the unstructured covariance matrix results in a lack of convergence then other covariance structures will be investigated. Toeplitz, First Order Autoregressive AR(1), and Compound Symmetry will be applied, in the specified order, until the model converges.

The estimated least-squares mean (LSM) for the change in GA area, and treatment difference of each GT005 dose against untreated control, as well as the corresponding 90% confidence interval, will be summarized by visit and treatment groups. A line plot for the estimated LSM with 90% CI by visit and treatment groups will also be provided.

As this study is being terminated, statistical modeling as described above and/or summary tables will be provided as appropriate based on data availability.

2.5.3 Handling of intercurrent events

The underlying question for the primary estimand is: what is the effect attributable to different doses of GT005 on GA change on FAF at Week 48 in subjects who have not received alternative GA medications or therapies in the study eye.

For this estimand, data following the below intercurrent event will be dealt with in the following specific way:

- Subject receives alternative GA medications or therapies in the study eye: GA lesion size data collected in the study eye after the subject initiates alternative GA medications or therapies will be censored and imputed assuming missing at random.

2.5.4 Handling of missing values not related to intercurrent event

In the case of missing data occurring in other scenarios, i.e. independent of intercurrent events defined in Table 1-2, the estimand based on an MAR approach will be considered specifically for each treatment arm the subjects are assigned.

2.5.5 Sensitivity analyses

Not applicable.

2.5.6 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

There are six secondary objectives:

1. Evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD
2. Evaluate the safety and tolerability of GT005
3. Evaluate the effect of GT005 on retinal anatomical measures
4. Evaluate the effect of GT005 on functional measures, BCVA and LLD
5. Evaluate the effect of GT005 on visual function, MNRead and FRI
6. Evaluate the effect of GT005 on patient-reported outcomes

2.6.1 Secondary endpoint(s)

The corresponding secondary endpoints are:

1. Change from baseline through Week 96 in GA area as measured by FAF
2. Frequency of treatment emergent adverse event (AE) through Week 96
3. Change in retinal morphology on multimodal imaging through Week 96

4.a Change in best corrected visual acuity (BCVA) Score via the early treatment for diabetic retinopathy (ETDRS) chart through Week 96

4.b Change in low luminance difference (LLD) via the ETDRS chart through Week 96

5.a Change in reading performance as assessed by Minnesota low-vision reading test (MNRead) chart through Week 96

5.b Change in functional reading independence (FRI) index through Week 96

6. Change in quality of life measured on the visual function questionnaire-25 (VFQ-25) through Week 96

2.6.2 Statistical hypothesis, model, and method of analysis

1. Change from baseline through Week 96 in GA area as measured by FAF

   - MMRM as described in Section 2.5.2 will be applied to the change from baseline through Week 96 in GA area, with intercurrent events and missing data handled in the same way as for the primary estimand (Section 2.5.3).

     The estimated least-squares mean (LSM) for the change in GA area, and treatment difference against untreated control, as well as the corresponding 90% confidence interval, will be summarized by visit and treatment groups. A line plot for the estimated LSM with 90% CI by visit and treatment groups will also be provided. All assessments of GA area will be listed by treatment group, site, and subject.

2. Frequency of treatment emergent adverse event (AE) through Week 96

[redacted]

- The summary tables for treatment-emergent serious AE (TESAE) will be presented as described in Section 2.7.1.
- Subjects who did not receive treatment due to surgical procedure related AEs will be listed separately by treatment group.

3. Change in retinal morphology on multimodal imaging through Week 96

- The presence of the following retinal morphology will be summarized based on observed data by visit for the number and percentage of subjects in reported categories:
    i. Junctional zone of GA (Increased FAF, Normal FAF, Not Applicable, Cannot Grade) assessed by FAF.
    ii. Junctional zone patterns (Atypical, Banded, Diffuse, Focal, Cannot Grade) assessed by FAF.

4.a Change in best corrected visual acuity (BCVA) Score via the early treatment for diabetic retinopathy (ETDRS) chart through Week 96

- The change in BCVA through Week 96 will be estimated among treatment groups via least squares means from a MMRM model. The model will include the change from baseline in BCVA measured by ETDRS as the dependent variable, BCVA at the baseline as the covariate, assessment visit, treatment group, two interaction terms (assessment visit and treatment group, assessment visit and BCVA at the baseline) as the fixed effect and participant as a random effect. The estimated least-squares mean (LSM) for the change in BCVA, and treatment difference against untreated control, as well as the corresponding 90% confidence interval, will be summarized by visit and treatment groups. A line plot for the estimated LSM with 90% CI by visit and treatment groups will also be provided. All BCVA assessments will be listed by treatment group, site, and subject.

4.b Change in low luminance difference (LLD) via the ETDRS chart through Week 96

- The LLD and the changes from baseline will be summarized based on observed data by assessment visits and treatment group. All LLD assessments will be listed by treatment group, site, and subject.

5.a Change in reading performance as assessed by Minnesota low-vision reading test (MNRead) chart through Week 96

- The Maximum reading speed (MRS) for each eye as assessed by MNRead Chart and the change from baseline will be summarized based on observed data by visit and treatment group. Reading speed (words per minute) will be computed for each of the 19 sentences read using the following formula:

$$60 \times max(0,10 - number\ of\ errors)/reading\ time\ in\ seconds$$

The mean of three higher reading speeds will be reported as the maximum reading speed.

5.b Change in functional reading independence (FRI) index through Week 96

- The FRI index and the changes from baseline will be calculated and summarized based on observed data by assessment visits and treatment group.

6. Change in quality of life measured on the visual function questionnaire-25 (VFQ-25) through Week 96

- The VFQ-25 sub-scales and composite scores and the changes from baseline will be calculated and summarized based on observed data by assessment visits and treatment group.

As this study is being terminated, statistical modeling and/or summary tables for corresponding endpoints will be provided as appropriate based on data availability.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data handling of secondary analyses for different endpoints are specified in Section 2.6.2.

2.7 Safety analyses

For all safety analyses, the FAS will be used. All listings and tables will be presented by the treatment group.

2.7.1 Adverse events (AEs)

Only AEs that occurred during the study period (from the date of randomization to the end of study) will be summarized. AEs recorded after screening but before the date of randomization will be listed only.

Treatment-emergent Adverse Event (TEAE): An adverse event is considered treatment emergent if the start date/time of the event is on or after the date of randomization, irrespective of the treatment arm. The primary summaries of AEs will be based on TEAEs.

The number (and percentage) of subjects with AEs will be summarized separately for ocular (study eye and fellow eye) and non-ocular events by treatment group in the following ways unless otherwise specified:

- Overall summary of death, subjects with any AE, any severe AE, any study treatment-related AE, any surgical procedure related AE, any AE leading to study discontinuation, any serious AE (SAE), any study treatment-related SAE, any surgical procedure related SAE, any SAE leading to study discontinuation
- AEs by primary SOC and PT
- AEs related to study treatment by SOC and PT (separately for study eye and non-ocular)
- AEs related to surgical procedure by SOC and PT (separately for study eye and non-ocular)
- SAEs by primary SOC and PT

- SAEs related to study treatment by SOC and PT (separately for study eye and non-ocular)
- SAEs related to surgical procedure by SOC and PT (separately for study eye and non-ocular)

A subject with multiple adverse events within a primary SOC is only counted once towards the total of the primary SOC.

All AEs, deaths, and SAEs (including those from the pre- and post-treatment periods) will be listed and those collected after the use of alternative GA therapies/medications, or during the pre-treatment, post-study period will be flagged. In addition, subjects who are not receiving treatment due to surgical procedure-related AEs will be listed separately by treatment group.

The MedDRA version used for reporting the AEs will be described in footnote.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on "on-treatment/treatment emergent" adverse events which are not serious adverse events with an incidence greater than 2% (or other cutting point as appropriate) and on "on-treatment/treatment emergent" serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population (i.e., the FAS of this study).

If for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE /SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. AESIs should also be assessed as to whether it fits the criteria of an SAE and reported appropriately. AESI should be reported as per reporting requirements [Protocol Section 8.3]. [redacted]

- [redacted]
- [redacted]

[redacted]

The number and percentage of subjects with AESIs will be summarized separated for ocular (study eye and fellow eye) events by category, PT, and treatment groups. In addition, AESIs related to the study treatment and/or surgical procedure will be summarized by category, PT and treatment groups.

2.7.2 Deaths

All deaths will be summarized by primary SOC and PT. A listing will also be provided.

2.7.3 Loss in best corrected visual acuity

The number and the percentage of subjects who lost ≥ 15/ ≥ 30 letters in BCVA from baseline up to Week 96 will be presented for the study eye and the fellow eye. Missing data will not be imputed.

2.7.4 Laboratory data

Laboratory parameters listed in Table 2-1 will be presented graphically using boxplots of absolute change from baseline values by treatment group and visit. No summary by visit tables will be provided.

A summary table with number and percentage of subjects satisfying the criteria representing clinically relevant abnormalities defined in Table 2-1 at any visit will be presented. A listing of subjects satisfying at least one criterion in Table 2-1 at any visit will also be presented.

Table 2-1 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

2.7.5 Other safety data

2.7.5.1 ECG and cardiac imaging data

No applicable.

2.7.5.2 Vital signs

A listing of subjects satisfying at least one criterion in Table 2-2 at any visit will be presented.

Table 2-2 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

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Functional Reading Independence (FRI) Index

The FRI index is a new patient-reported outcome measure developed specifically for use in GA patients. The FRI index evaluates the level of independence patients have in performing everyday activities that require reading, such as writing a cheque or reading a prescription. Scores derived from the index range from 1 (unable to do) to 4 (total independence).

The composite score is the sum of the seven sub-questions.

If responses are missing for main questions or sub-questions, scores may be imputed based on the scoring for missing items algorithm provided in Table 2-3 below.

Table 2-3 Scoring Missing FRI Items

Question or Sub-Question with Missing Data	Missing Response within Context of other Sub-Questions	Coding and Imputation

Main Questions 1–7	If missing main question and responses of "Yes" or "No" to sub-questions a-e…	Impute "Yes" to main question and score according to algorithm
	If missing main question and "Your vision" or "For other reasons" to sub-question g….	Impute "No" to main question and score according to algorithm
	If missing main question and no responses to any sub-questions…	Code as "missing"
Sub-questions a–c	If missing sub-questions a-c…	Code as "missing" and score according to algorithm
Sub-question d	If missing sub-question d and "No" response to all sub-questions a-c…	Impute "No" for sub-question d and score according to algorithm
Sub-question e	If "Yes" to performing activity and "missing" for sub-question e and no responses to sub-question f…	Impute "No" for sub-question e and score according to algorithm
	If "Yes" to performing activity and "missing" for sub-question e and response of "Some of the time", "Most of the time" or "All of the time" to sub-question f…	Impute "yes" for sub-question e and score according to algorithm
Sub-question f	If "Yes" to performing activity, "Yes" to sub-question e and "missing" for sub-question f…	Impute "Some of the time" for sub-question f and score according to algorithm
Sub-question g	If "No" to main question and "missing" for sub-question g…	Impute "For other reasons" for sub-question g and score according to algorithm

Visual Function Questionnaires (VFQ-25)

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 sub-scales and composite scores and changes from baseline will be calculated and summarized by assessment visits. Each subscale score has a range of 0 to 100 inclusive and will be calculated from the re-scaled raw data as described in Table 2-4. A missing response will not be re-scaled (except for the response to question 15c, see below, which will be re-set to 0 if the response to question 15b is 1).

Table 2-4 Rescaling of VFQ-25 questions

Answer to question	Rescaling for questions 1, 3, 4 and 15c	Rescaling for question 2	Rescaling for questions 5-14, 16 and 16a	Rescaling for questions 17-25
1	100	100	100	0

2	75	80	75	25
3	50	60	50	50
4	25	40	25	75
5	0	20	0	100
6	N/A	0	N/A*	N/A

Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing
If 15b=3, then 15c should be recoded to missing
*Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing".

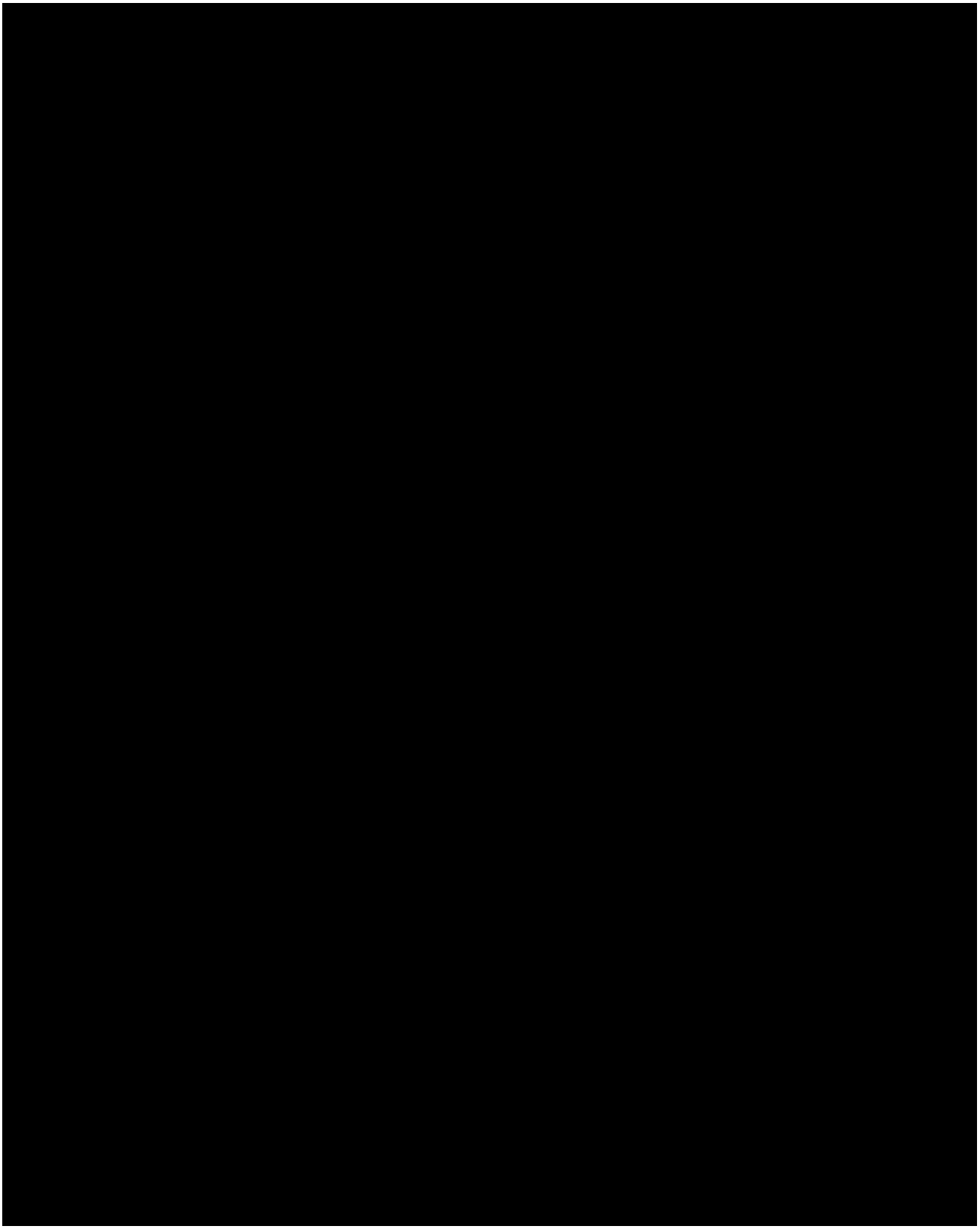
The subscale scores are then calculated according to Table 2-5.

Table 2-5 Questions contributing to VFQ-25 subscales

Subscale	Questions
General vision	2
Ocular pain	4 and 19
Near activities	5, 6 and 7
Distance activities	8, 9 and 14
Social functioning	11 and 13
Mental health	3, 21, 22 and 25
Role difficulties	17 and 18
Dependency	20, 23 and 24
Driving	15c, 16 and 16a
Color vision	12
Peripheral vision	10

The composite score is the average of the 11 subscales shown in Table 2-5. It will be set to missing if at least six of the subscales are missing.

[redacted]



[redacted]

3 Sample size calculation

Untreated control mean GA change at 48 weeks was assumed to be 2.1 mm^2 with standard deviation (SD) =1.3 mm^2. The following hypotheses are considered:

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

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

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

[redacted]

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

4 Change to protocol specified analyses

The Week 48 interim analysis was removed.

The Safety Analysis Set (SAF) was removed.

The estimand framework was simplified. Analysis for the primary endpoint was changed to MMRM.

Subgroup of interest is not applicable.

5 Appendix

Statistical methods are described in the main part of the clinical study report. This appendix provides further details on missing data imputation, statistical methods, and statistical derivation.

5.1 Imputation rules

The general approach to handling missing dates is shown below for dates of AEs, medical history diagnosis, and concomitant treatment. The imputation of missing dates for surgery or procedures will use the same rules as for concomitant treatment.

The detailed algorithms will appear in Programming Dataset Specifications.

For the purpose of date imputation, the treatment follow-up period date is defined as the last available visit date.

5.1.1 AE date imputation

5.1.1.1 Adverse event end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death, cut-off date if available).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (the last visit date, last day of the month, date of death, cut-off date if available).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.
4. In case the imputed AE end date is before AE start date, then use AE start date as imputed AE end date.

5.1.1.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year

Partial Adverse Event Start Date	Not used	MON	YYYY
Randomization Date	Not used	RANDM	RANDY

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < RANDM**	**MON = RANDM**	**MON > RANDM**
YYYY	**(1)**	**(1)**	**(1)**	**(1)**
MISSING	No convention	No convention	No convention	No convention
YYYY < TRTY	**(2.a)**	**(2.b)**	**(2.b)**	**(2.b)**
	Before Randomization	Before Randomization	Before Randomization	Before Randomization
YYYY = TRTY	**(4.a)**	**(4.b)**	**(4.c)**	**(4.c)**
	Uncertain	Before Randomization	Uncertain	After Randomization
YYYY > TRTY	**(3.a)**	**(3.b)**	**(3.b)**	**(3.b)**
	After Randomization	After Randomization	After Randomization	After Randomization

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < randomization date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = randomization date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the randomization date year value, the AE started before randomization. Therefore:
    a. If AE day and month are missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. If AE month is missing but day is not missing, the observed start date will be used with month imputed as JulYYYY.
    c. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the randomization date year value, the AE started after randomization. Therefore:
    a. If the AE day and month are missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. If AE month is missing but day is not missing, the observed start date will be used with month imputed as JulYYYY.
    c. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the randomization date year value:
    a. And the AE day and month are missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. If AE month is missing and day is not missing, the observed start date will be used with month imputed as the reference start month.

c. Else if the AE month is less than the randomization month, the imputed AE start date is set to the mid-month point (15MONYYYY).
d. Else if the AE month is equal to the randomization date month or greater than the randomization date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant treatment end date imputation

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of the last study visit date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of the last study visit date and the end of the year (31DECYYYY).
3. Only include if ongoing records will have an imputed CM end date. If CM day/month/year is missing then use the the last study visit date + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.
5. If imputed CM end date is greater than date of death, date of cutoff, or the last visit date, then use the minimum of date of death, date of cutoff, and the last visit date as the imputed CM end date.

5.1.2.2 Concomitant treatment start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Randomization Date	Not used	RANDM	RANDY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < RANDM	MON = RANDM	MON > RANDM
YYYY MISSING	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain
YYYY < TRTY	**(2.a)** Before Randomization	**(2.b)** Before Randomization	**(2.b)** Before Randomization	**(2.b)** Before Randomization
YYYY = TRTY	**(4.a)** Uncertain	**(4.b)** Before Randomization	**(4.a)** Uncertain	**(4.c)** After Randomization
YYYY > TRTY	**(3.a)** After Randomization	**(3.b)** After Randomization	**(3.b)** After Randomization	**(3.b)** After Randomization

If the CM start date year value is missing, the imputed CM start date is set to one day prior to randomization date.

If the CM start date year value is less than the randomization date year value, the CM started before randomization. Therefore:

a. If the CM day and month are missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
b. If CM month is missing but day is not missing, the observed start date will be used with month imputed as JulYYYY.
c. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

If the CM start date year value is greater than the randomization date year value, the CM started after randomization. Therefore:

a. If the CM day and month are missing, the imputed CM start date is set to the year start point (01JanYYYY).
b. If CM month is missing but day is not missing, the observed start date will be used with month imputed as JanYYYY.
c. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

If the CM start date year value is equal to the randomization date year value:

a. And the CM day and CM month are missing or the CM day is missing and CM month is equal to the randomization date month, then the imputed CM start date is set to one day prior randomization date.
b. Else if the CM month is less than the randomization date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
c. Else if the CM month is greater than the randomization date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.2.3 Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the randomization date.

- If DIAG year < randomization date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
  - else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = randomization date year
  - and (DIAG month is missing OR DIAG month is equal to randomization month), the imputed DIAG date is set to one day before randomization date
  - else if DIAG month < randomization month, the imputed DIAG date is set to the mid-month point (15MON YYYY)
  - else if DIAG month > randomization month => data error
- If DIAG year > randomization date year => data error

5.1.2.4 Other imputations

Not applicable.

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The below severity grade will be used in this study:

- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

The following MMRM will be used for the primary efficacy endpoint. The model will include the change from baseline in GA area measured by FAF as the dependent variable, GA area at the baseline as the covariate, assessment visit, treatment group, two interaction terms (assessment visit and treatment group, assessment visit and GA area at the baseline) as the fixed effect and participant as a random effect.

For this analysis, the data structure is one record per subject per scheduled visit. The data will include all subjects and have records for all scheduled visits, regardless of whether the assessment was missed or not at a given visit. Missing values will not be imputed and will be passed to the model as missing. The SAS PROC MIXED will be used to perform the analysis.

5.5 Rule of exclusion criteria of analysis sets

The below classification of non-PDs will be used for the analysis sets.

Table 5-1 Subject Classification

Analysis Set	Non-PD criteria that cause subjects to be excluded
All Enrolled Set	Not signed the informed consent
Full Analysis Set	Not randomized