

**Sponsor**

Gyroscope Therapeutics

Generic Drug Name

GT005 / PPY988

Trial Indication(s)

Geographic atrophy secondary to age-related macular degeneration.

Protocol Number

GT005-02

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: July 14, 2020 (Actual)

Primary Completion Date: April 05, 2024 (Actual)

Study Completion Date: April 05, 2024 (Actual)

Reason for Termination (If applicable)

Terminated for interim analysis demonstrating futility (trial highly unlikely to meet efficacy outcome). The trial is not ending early because of medical problems or concerns.

Study Design/Methodology

This was a Phase II, outcomes assessor-masked, multicentre, randomized study to assess 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 were planned to be randomized to GT005 or the untreated control group.

Subjects entered the study had genotyping and serum Complement factor I (Gene / PROTEIN) (CFI) levels assessed. Assessments were either performed at a sponsor-approved laboratory during the EXPLORE screening period or provided through participation in a previous Gyroscope sponsored study. If subjects failed to meet the eligibility criteria for EXPLORE, they were classified as screen failures for this study and could be considered for entry into another Novartis/Gyroscope sponsored study.

After providing the informed consent, subjects underwent ophthalmic and clinical assessments to determine eligibility for inclusion in the study.

Upon confirmation of eligibility, subjects in part 1 were randomized to one of two groups: low dose [2E10 vg], or high dose [2E11 vg]. Within each group, subjects were allocated to GT005 or untreated control based on a 2:1 ratio. Once part 1 enrolment was completed, and the last active subject completed screening and either was screen-failed or randomized, then Part 2 could commence. In part 2, subjects were randomized to the low dose [2E10] group or untreated control based on a 2:1 ratio. The study eye was identified for all subjects.

Subjects were stratified by GA lesion size on Fundus autofluorescence (FAF) (≤ 10 mm² or > 10 mm²) and presence of Choroidal neovascular AMD (CNV) in the fellow eye (Yes or No). Randomization of study eyes in the GA lesion size upper stratum of > 10 mm² to 17.5 mm² was capped at 20% of total subjects randomized. Once enrolment capping at 20% based on the upper GA lesion size was reached, eyes that fulfilled the cap criteria were no longer eligible, unless the subject had a CFI rare variant genotype (minor allele frequency $\leq 1\%$) previously associated with normal or low serum CFI or had an unreported CFI rare variant genotype. Of all subjects enrolled and randomized in the study, the presence of CNV in the fellow eye was capped at 25% per stratum. A permuted-block randomization method was used to obtain an approximately 2:1 ratio between GT005 and the untreated control groups for each dose group within each stratum.

Following randomization, the investigator was informed of the subject's allocated treatment (GT005 or the untreated control group) and the study eye selected. To minimize bias, all imaging endpoint assessments and grading were performed at a Central Reading Centre (CRC), in a masked fashion.

For part 1, the Sponsor, subject, investigators, and study personnel performing clinical assessments remained masked to dose received for those allocated to GT005. For part 2, the Sponsor, investigators, subjects, and study personnel performing clinical assessments were unmasked to dose received, since only the low dose was administered.

Subjects randomized to GT005 underwent a single time subretinal administration of the study drug. Vitreous samples were collected during surgery. Following surgery, a prophylactic steroid regimen was prescribed.

The study consisted of a screening period lasting up to 8 weeks (or up to 12 weeks if agreed by the Sponsor Medical Monitor), followed by a 96-week study period. All subjects were assessed for the occurrence of Adverse event(s) (AEs) at each visit and underwent functional visual and retinal imaging, anatomical assessments, and biological sampling as per the schedule of assessments.

This study was conducted in compliance with Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), informed consent regulations, the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) Guidelines, and the Food and Drug Administration (FDA) guidance.

On 24-Aug-2023, the decision was taken to terminate the study and the GT005 program. The decision was aligned with the recommendation of an independent Data Monitoring Committee (DMC), which concluded that futility criteria had been met for the HORIZON study (GT005-03) and the overall benefit-risk ratio did not support continuation of the current development program as planned. All GT005-treated subjects, who were willing to be transferred into the long-term safety follow-up study were enrolled in the ORACLE (CPPY988A12203B / NCT05481827) study.

Centers

55 centers in 8 countries: United States(32), Australia(2), France(3), Germany(5), Netherlands(1), Poland(1), Spain(5), United Kingdom(6)

Objectives:

To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD

To evaluate the effect of GT005 on the progression of GA in subjects with GA due to AMD

To evaluate the safety and tolerability of GT005

To evaluate the effect of GT005 on retinal anatomical measures

To evaluate the effect of GT005 on functional Measures

To evaluate the effect of GT005 on visual Function

To evaluate the effect of GT005 on patient reported outcomes

Test Product (s), Dose(s), and Mode(s) of Administration

GT005 is a recombinant, non-replicating AAV2 expressing human CFI. GT005 was assessed at two doses; low dose (2E10 vg) and high dose (2E11 vg) in part 1; and low dose (2E10 vg) in part 2. GT005 was administered as a single time subretinal

injection into the study eye of subjects allocated to one of the two GT005 doses. Subjects allocated to GT005 treatment were injected with GT005 across one or more bleb(s). Subjects allocated to the untreated control group did not receive any treatment.

Statistical Methods

The following analysis sets were used in this study:

- The All-Enrolled Set included all subjects who had signed informed consent.
- The Full Analysis Set (FAS) included all subjects who were randomized to GT005 or untreated control. The FAS was used for the analysis of efficacy and safety data.

Analysis of primary endpoint:

The primary endpoint was estimated among treatment groups via least-squares means from a Mixed Model Repeated Measures (MMRM) analysis. 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 (CI), were summarized and plotted. The missing at random (MAR) approach was applied for imputing missing data related to intercurrent events. As the majority of part 2 subjects discontinued the study due to study terminated by sponsor, the MAR assumption was not suitable. Therefore, the MMRM analysis was only performed in part 1.

Analysis of secondary endpoints:

- Change from baseline through Week 96 in GA area as measured by FAF was evaluated in the same way as for primary endpoint for part 1.
- Change in retinal morphology on multimodal imaging through Week 96 was summarized based on observed data in following categories:
 - Junctional zone of GA (Increased FAF, Normal FAF, Not Applicable, Cannot Grade) assessed by FAF.
 - Junctional zone patterns (Atypical, Banded, Diffuse, Focal, Cannot Grade) assessed by FAF.

Change in Best corrected visual acuity (BCVA) Score via the Early treatment diabetic retinopathy study scale (ETDRS) chart through Week 96 was estimated among treatment groups via LS means from a MMRM model for part 1. The estimated LSM for the change in BCVA, and treatment difference against untreated control, as well as the corresponding 90% CI, were summarized and plotted.

- Change in Low luminance difference (LLD) via the ETDRS chart through Week 96 was summarized based on observed data.
- Change in reading performance as assessed by Minnesota low-vision reading (test) (MNRead) chart through Week 96 was summarized based on observed data.
- Summary statistics were provided for the Functional reading independence (FRI) index composite score and the Visual function questionnaire (VFQ)-25 composite score and subscales.

All summary statistics were presented separately for part 1 and part 2.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Able and willing to give written informed consent
2. Age ≥ 55 years
3. Have a clinical diagnosis of GA secondary to AMD in the study eye, as determined by the Investigator, and a diagnosis of AMD in the contralateral eye (except if the subject is monocular)
4. Have GA lesion(s) total size between or equal to 1.25mm² to 17.5mm² in the study eye
5. The GA lesion(s) in the study eye must reside completely within the FAF image
6. Up to 25% of the enrolled study population are permitted to have CNV in the fellow eye, defined as either:
 - a. Non-exudative/sub-clinical fellow eye CNV identified at Screening, or
 - b. Known history of fellow eye CNV with either ≥ 2 years since diagnosis or with no active treatment required in 6 months prior to Screening
7. Have a BCVA of 24 letters (6/95 and 20/320 Snellen acuity equivalent) or better, using ETDRS charts, in the study eye
8. Part 1 Only: Subjects carrying a CFI rare variant genotype (minor allele frequency of $\leq 1\%$) previously associated with low serum CFI or subjects carrying an unreported CFI rare variant genotype that have tested to have a low serum CFI
9. Able to attend all study visits and complete the study procedures
10. Women of child-bearing potential must have a negative pregnancy test within 2 weeks prior to randomisation. A pregnancy test is

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

Exclusion Criteria:

- 1) Subjects who have a clinical diagnosis of Stargardt Disease or other retinal dystrophies, confirmed by the central reading centre
- 2) Have a history, or evidence, of CNV in the study eye
- 3) Presence of moderate/severe or worse non-proliferative diabetic retinopathy in the study eye
- 4) Have history of vitrectomy, sub-macular surgery, or macular photocoagulation in the study eye
- 5) History of intraocular surgery in the study eye within 12 weeks prior to Screening (Visit 1). Yttrium aluminium garnet capsulotomy is permitted if performed >10 weeks prior to Visit 1
- 6) Have clinically significant cataract that may require surgery during the study period in the study eye
- 7) Presence of moderate to severe glaucomatous optic neuropathy in the study eye; uncontrolled IOP despite the use of two or more topical agents; a history of glaucoma-filtering or valve surgery is also excluded
- 8) Axial myopia of greater than -8 dioptres in the study eye
- 9) Have any other significant ocular or non-ocular medical or psychiatric condition which, in the opinion of the Investigator, may either put the subject at risk or may influence the results of the study
- 10) Have a contraindication to specified protocol corticosteroid regimen
- 11) Have received any investigational and/or approved product(s) for the treatment of GA within the past 6 months, or 5 half-lives (whichever is longer) other than nutritional supplements such as the age-related eye disease study (AREDS) formula in the study eye or systemically
- 12) Have received a gene or cell therapy at any time

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

14) Active malignancy within the past 12 months, except for: appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or prostate cancer with a stable prostate-specific antigen (PSA) ≥ 12 months

Participant Flow Table

Overall Study

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control	Total
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.	
Started	52	9	37	98
Randomized Part 1	10	9	14	33
Randomized Part 2	42	0	23	65
Randomized and treated Part 1	9	9	0	18
Randomized and treated Part 2	18	0	0	18
Completed	6	8	7	21
Not Completed	46	1	30	77
Death	3	0	2	5
Study terminated by sponsor	16	1	25	42
Withdrawal by Subject	4	0	3	7
Sponsor instructions	23	0	0	23

Baseline Characteristics

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control	Total
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.	
Number of Participants [units: participants]	52	9	37	98
Baseline Analysis Population Description				
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation				
	76.8±7.33	72.7±8.96	75.2±7.07	75.8±7.41
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
American Indian or Alaska Native	1	0	0	1
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	0	0	0
White	51	7	35	93
More than one race	0	0	0	0
Unknown or Not Reported	0	2	2	4
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	34	5	18	57

Male

18

4

19

41

Primary Outcome Result(s)

The change from baseline to Week 48 in geographic atrophy (GA) - Part 1

Description The change from baseline to Week 48 in GA area as measured by fundus autofluorescence (FAF)

Time Frame Baseline, Weeks 12, 24, 36, and 48

Analysis Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

Population

Description

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	8	12
The change from baseline to Week 48 in geographic atrophy (GA) - Part 1 (units: mm²)	Least Squares Mean ± Standard Error	Least Squares Mean ± Standard Error	Least Squares Mean ± Standard Error
Part 1 Week 12 (n=9,8,12)	0.773 ± 0.2151	0.764 ± 0.2159	0.482 ± 0.1848
Part 1 Week 24 (n=9,7,9)	1.338 ± 0.2763	1.519 ± 0.2845	0.680 ± 0.2500
Part 1 Week 36 (n=6,7,10)	1.800 ± 0.3740	2.044 ± 0.3669	1.132 ± 0.3229
Part 1 Week 48 (n=5,8,10)	2.120 ± 0.3726	2.378 ± 0.3414	1.144 ± 0.3040

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 12
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	0.291	
Standard Error of the mean	0.2838	
90 % Confidence Interval 2-Sided	-0.195 to 0.777	

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 12
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	0.282	
Standard Error of the mean	0.2843	
90 % Confidence Interval 2-Sided	-0.206 to 0.769	

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 24
Type of Statistical Test	Superiority	

Method	Other mixed model repeated measures
Other LS Mean Difference	0.658
Standard Error of the mean	0.3730
90 % Confidence Interval 2-Sided	0.017 to 1.299

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 24
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	0.840	
Standard Error of the mean	0.3791	
90 % Confidence Interval 2-Sided	0.189 to 1.490	

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 36
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	0.668	
Standard Error of the mean	0.4954	

90
% Confidence Interval
2-Sided

-0.177 to 1.512

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 36
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	0.912	
Standard Error of the mean	0.4887	

90
% Confidence Interval
2-Sided

0.078 to 1.746

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 48
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	0.976	
Standard Error of the mean	0.4813	

90
% Confidence Interval
2-Sided

0.150 to 1.803

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 48
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	1.233	
Standard Error of the mean	0.4573	
90 % Confidence Interval 2-Sided	0.445 to 2.022	

Secondary Outcome Result(s)

The change from baseline in geographic atrophy (GA) at Week 72 and Week 96 - Part 1

Description	The change from baseline to Week 48 in GA area as measured by fundus autofluorescence (FAF)
Time Frame	Baseline, Weeks 72 and 96
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	6	8	9

The change from baseline in geographic atrophy (GA) at Week 72 and Week 96 - Part 1 (units: mm ²)	Least Squares Mean ± Standard Error	Least Squares Mean ± Standard Error	Least Squares Mean ± Standard Error
Part 1 Week 72 (n=5,7,9)	3.643 ± 0.9725	3.149 ± 0.9150	1.875 ± 0.8273
Part 1 Week 96 (n=6,8,7)	4.837 ± 1.0712	4.074 ± 1.0305	2.796 ± 0.9240

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 72
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	1.769	
Standard Error of the mean	1.2808	
90 % Confidence Interval 2-Sided	-0.441 to 3.979	

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 72
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	1.274	
Standard Error of the mean	1.2349	

90
% Confidence Interval
2-Sided

-0.863 to 3.412

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 96
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	2.041	
Standard Error of the mean	1.4177	

90
% Confidence Interval
2-Sided

-0.386 to 4.468

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 96
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean	1.278	
Standard Error of the mean	1.3857	

90
% Confidence Interval
2-Sided

-1.099 to 3.655

Summary of Adverse Events

Description	An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject. A TEAE is defined as any AE that develops after randomization or any AE already present that worsens following randomization. The primary summaries of AEs are based on TEAEs.
Time Frame	Adverse events are reported from randomization up to end of study, for a maximum timeframe of approximately 96 weeks.
Analysis Population Description	Full Analysis Set - all randomized participants

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	52	9	37
Summary of Adverse Events (units: Participants)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)
Subjects with at least one ocular adverse event for the study eye	18 (34.62%)	9 (100%)	2 (5.41%)
Subjects with at least one ocular adverse event for the fellow eye	6 (11.54%)	3 (33.33%)	5 (13.51%)
Subjects with at least one non-ocular adverse event	13 (25%)	8 (88.89%)	14 (37.84%)
Subjects with at least one ocular adverse event related to study treatment for the study eye	3 (5.77%)	4 (44.44%)	0 (%)
Subjects with at least one non-ocular adverse event related to study treatment	0 (%)	0 (%)	0 (%)
Subjects with at least one ocular adverse event related to surgical procedure for the study eye	12 (23.08%)	7 (77.78%)	0 (%)
Subjects with at least one non-ocular adverse event related to surgical procedure	0 (%)	0 (%)	0 (%)

Subjects with at least one ocular adverse event related to study procedure for the study eye	1 (1.92%)	1 (11.11%)	0 (%)
Subjects with at least one non-ocular adverse event related to study procedure	1 (1.92%)	0 (%)	0 (%)
Subjects with at least one ocular adverse event leading to study discontinuation for the study eye	0 (%)	0 (%)	0 (%)
Subjects with at least one non-ocular adverse event leading to study discontinuation	3 (5.77%)	0 (%)	2 (5.41%)
Subjects with at least one ocular adverse event of special interest for the study eye	4 (7.69%)	7 (77.78%)	0 (%)
Subjects with at least one ocular adverse event of special interest for the fellow eye	0 (%)	0 (%)	1 (2.7%)
Subjects with at least one ocular serious adverse event (SAE) for the study eye	1 (1.92%)	0 (%)	0 (%)
Subjects with at least one ocular serious adverse event for the fellow eye	0 (%)	0 (%)	0 (%)
Subjects with at least one non-ocular serious adverse event	5 (9.62%)	2 (22.22%)	4 (10.81%)
Subjects with at least one ocular serious adverse event related to study treatment for the study eye	0 (%)	0 (%)	0 (%)
Subjects with at least one non-ocular serious adverse event related to study treatment	0 (%)	0 (%)	0 (%)
Subjects with at least 1 ocular SAE related to surgical procedure - study eye	0 (%)	0 (%)	0 (%)
Subjects with at least one non-ocular serious adverse event related to surgical procedure	0 (%)	0 (%)	0 (%)
Subjects with at least one ocular serious adverse event related to study procedure for the study eye	0 (%)	0 (%)	0 (%)
Subjects with at least one non-ocular serious adverse event related to study procedure	0 (%)	0 (%)	0 (%)
Subjects with at least 1 ocular SAE event leading to study discontinuation- study eye	0 (%)	0 (%)	0 (%)

Subjects with at least one non-ocular serious adverse event leading to study discontinuation	3 (5.77%)	0 (%)	2 (5.41%)
Deaths	3 (5.77%)	0 (%)	2 (5.41%)

Ocular adverse events by primary system organ class and preferred term for the study eye

Description	An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject. A TEAE is defined as any AE that develops after randomization or any AE already present that worsens following randomization. The primary summaries of AEs are based on TEAEs. System organ classes are sorted alphabetically, and preferred terms are sorted by decreasing overall frequency within system organ class.
Time Frame	Adverse events are reported from randomization up to end of study, for a maximum timeframe of approximately 96 weeks.
Analysis Population Description	Full Analysis Set - all randomized participants

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	52	9	37
Ocular adverse events by primary system organ class and preferred term for the study eye (units: Participants)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)
Subjects with at least one event	18 (34.62%)	9 (100%)	2 (5.41%)
Eye disorders	15 (28.85%)	9 (100%)	2 (5.41%)
-Retinal pigmentation	3 (5.77%)	6 (66.67%)	0 (%)

-Conjunctival haemorrhage	6 (11.54%)	1 (11.11%)	0 (%)
-Cataract	3 (5.77%)	2 (22.22%)	1 (2.7%)
-Cataract nuclear	2 (3.85%)	1 (11.11%)	0 (%)
-Eye pain	1 (1.92%)	2 (22.22%)	0 (%)
-Retinal haemorrhage	2 (3.85%)	1 (11.11%)	0 (%)
-Anterior chamber cell	1 (1.92%)	1 (11.11%)	0 (%)
-Blepharitis	2 (3.85%)	0 (%)	0 (%)
-Conjunctivitis allergic	1 (1.92%)	1 (11.11%)	0 (%)
-Anterior chamber flare	0 (%)	1 (11.11%)	0 (%)
-Choroidal detachment	0 (%)	1 (11.11%)	0 (%)
-Conjunctival hyperaemia	1 (1.92%)	0 (%)	0 (%)
-Dry eye	1 (1.92%)	0 (%)	0 (%)
-Eye pruritus	0 (%)	0 (%)	1 (2.7%)
-Hypotony maculopathy	0 (%)	1 (11.11%)	0 (%)
-Iridocyclitis	0 (%)	1 (11.11%)	0 (%)
-Iritis	1 (1.92%)	0 (%)	0 (%)

-Keratitis	1 (1.92%)	0 (%)	0 (%)
-Lacrimation increased	0 (%)	1 (11.11%)	0 (%)
-Macular hole	1 (1.92%)	0 (%)	0 (%)
-Meibomian gland dysfunction	1 (1.92%)	0 (%)	0 (%)
-Metamorphopsia	1 (1.92%)	0 (%)	0 (%)
-Ocular hypertension	1 (1.92%)	0 (%)	0 (%)
-Open angle glaucoma	0 (%)	1 (11.11%)	0 (%)
-Photophobia	0 (%)	1 (11.11%)	0 (%)
-Photopsia	1 (1.92%)	0 (%)	0 (%)
-Posterior capsule opacification	0 (%)	0 (%)	1 (2.7%)
-Punctate keratitis	1 (1.92%)	0 (%)	0 (%)
-Retinal depigmentation	1 (1.92%)	0 (%)	0 (%)
-Visual acuity reduced	1 (1.92%)	0 (%)	0 (%)
-Visual impairment	1 (1.92%)	0 (%)	0 (%)
-Visual snow syndrome	1 (1.92%)	0 (%)	0 (%)
-Vitreous floaters	1 (1.92%)	0 (%)	0 (%)

-Vitreous haemorrhage	1 (1.92%)	0 (%)	0 (%)
Injury, poisoning and procedural complications	4 (7.69%)	1 (11.11%)	0 (%)
-Post procedural discomfort	2 (3.85%)	0 (%)	0 (%)
-Procedural pain	1 (1.92%)	1 (11.11%)	0 (%)
-Suture related complication	1 (1.92%)	1 (11.11%)	0 (%)
Investigations	4 (7.69%)	3 (33.33%)	0 (%)
-Intraocular pressure increased	4 (7.69%)	3 (33.33%)	0 (%)
Skin and subcutaneous tissue disorders	1 (1.92%)	0 (%)	0 (%)
-Telangiectasia	1 (1.92%)	0 (%)	0 (%)

Non-ocular adverse events - summary

Description	An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject. A TEAE is defined as any AE that develops after randomization or any AE already present that worsens following randomization. The primary summaries of AEs are based on TEAEs.
Time Frame	Adverse events are reported from randomization up to end of study, for a maximum timeframe of approximately 96 weeks.
Analysis Population Description	Full Analysis Set - all randomized participants

GT005 Low Dose [2E10 vg]

GT005 High Dose [2E11 vg]

Untreated control

Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	52	9	37
Non-ocular adverse events - summary (units: Participants)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)
Subjects with at least one event	13 (25%)	8 (88.89%)	14 (37.84%)

Change in GA morphology from Baseline to Week 96 on colour fundus photography (CFP) - Number of participants with increase in Fundus autofluorescence - Part 1

Description	Change in GA morphology on multimodal imaging through Week 96
Time Frame	Baseline, Weeks 5,12,24,36,48,72,96
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	8	12
Change in GA morphology from Baseline to Week 96 on colour fundus photography (CFP) - Number of participants with increase in Fundus autofluorescence - Part 1 (units: Participants)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)
Part 1 Week 5 (n= 0,2,0)	(NaN%)	2 (100%)	(NaN%)

Part 1 Week 12 (n=9,8,12)	8 (88.89%)	8 (100%)	11 (91.67%)
Part 1 Week 24 (n=9,7,10)	8 (88.89%)	7 (100%)	10 (100%)
Part 1 Week 36 (n=6,7,10)	5 (83.33%)	7 (100%)	10 (100%)
Part 1 Week 48 (n=5,8,10)	5 (100%)	8 (100%)	10 (100%)
Part 1 Week 72 (n=5,8,9)	5 (100%)	8 (100%)	9 (100%)
Part 1 Week 96 (n=6,8,7)	6 (100%)	8 (100%)	7 (100%)

Change from Baseline to Week 48 in GA morphology on colour fundus photography (CFP) - Number of participants with increase in Fundus autofluorescence - Part 2

Description	Change in GA morphology on multimodal imaging through Week 48
Time Frame	Baseline, Weeks 5,12,24,36,48
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	17	0	20
Change from Baseline to Week 48 in GA morphology on colour fundus photography (CFP) - Number of participants with increase in Fundus	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)	Count of Participants (Not Applicable)

autofluorescence - Part 2
(units: Participants)

Part 2 Week 5 (n= 16,0, 0)	16 (100%)	(NaN%)	(NaN%)
Part 2 Week 12 (n=17,0,20)	17 (100%)	(NaN%)	20 (100%)
Part 2 Week 24 (n=17,0,11)	16 (94.12%)	(NaN%)	11 (100%)
Part 2 Week 36 (n=14,0,0)	13 (92.86%)	(NaN%)	(NaN%)
Part 2 Week 48 (n=5,0,0)	5 (100%)	(NaN%)	(NaN%)

Change in Best corrected visual acuity (BCVA) Score from Baseline through Week 96 via the early treatment for diabetic retinopathy (ETDRS) chart - Part 1

Description	BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.
Time Frame	Baseline, Weeks 1, 5, 8, 12, 24, 36, 48, 72 and 96
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	9	12
Change in Best corrected visual acuity (BCVA) Score from Baseline through Week 96 via the early treatment for diabetic retinopathy (ETDRS) chart -	Least Squares Mean ± Standard Error	Least Squares Mean ± Standard Error	Least Squares Mean ± Standard Error

Part 1

(units: Letters read)

Part 1 - Week 1 (n=9,9,0)	-4.7 ± 4.04	-5.2 ± 4.27	
Part 1 - Week 5 (n=8,9,0)	-1.7 ± 4.08	-7.6 ± 4.26	
Part 1 - Week 8 (n=9,9,0)	-1.6 ± 4.03	-4.5 ± 4.23	
Part 1 - Week 12 (N=9,9,12)	-2.3 ± 4.03	-7.5 ± 4.18	-1.2 ± 3.81
Part 1 - Week 24 (n=9,9,10)	-5.6 ± 4.03	-12.0 ± 4.18	-0.4 ± 3.87
Part 1 - Week 36 (n=8,8,10)	-10.0 ± 4.10	-12.9 ± 4.28	-1.0 ± 3.89
Part 1 - Week 48 (n=5,8,10)	-8.6 ± 4.52	-13.3 ± 4.32	-5.7 ± 3.91
Part 1 - Week 72 (n=5,8,10)	-6.3 ± 4.56	-9.6 ± 4.34	-8.9 ± 3.94
Part 1 - Week 96 (n=6,8,7)	-6.5 ± 4.50	-11.0 ± 4.33	-7.9 ± 4.30

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 12
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-1.1	
Standard Error of the mean	5.49	
90 % Confidence Interval 2-Sided	-10.3 to 8.1	

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 12
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Type of Statistical Test	Superiority
Method	Other mixed model repeated measures
Other LS Mean Difference	-6.3
Standard Error of the mean	5.96
90 % Confidence Interval 2-Sided	-16.3 to 3.7

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 24
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-5.2	
Standard Error of the mean	5.54	
90 % Confidence Interval 2-Sided	-14.5 to 4.1	

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 24
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	

Other LS Mean Difference	-11.7
Standard Error of the mean	6.00
90 % Confidence Interval 2-Sided	-21.7 to -1.6

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 36
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-9.0	
Standard Error of the mean	5.63	
90 % Confidence Interval 2-Sided	-18.4 to 0.5	

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 36
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-11.9	
Standard Error of the mean	6.08	

90
% Confidence Interval
2-Sided

-22.1 to -1.7

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 48
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-2.9	
Standard Error of the mean	5.88	

90
% Confidence Interval
2-Sided

-12.7 to 6.9

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 48
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-7.6	
Standard Error of the mean	6.14	

90
% Confidence Interval
2-Sided

-17.9 to 2.7

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 72
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	2.6	
Standard Error of the mean	5.96	
90 % Confidence Interval 2-Sided	-7.4 to 12.5	

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 72
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-0.7	
Standard Error of the mean	6.18	
90 % Confidence Interval 2-Sided	-11.1 to 9.6	

Statistical Analysis

Groups	GT005 Low Dose [2E10 vg], Untreated control	Week 96
Type of Statistical Test	Superiority	

Method	Other mixed model repeated measures
Other LS Mean Difference	1.4
Standard Error of the mean	6.07
90 % Confidence Interval 2-Sided	-8.7 to 11.5

Statistical Analysis

Groups	GT005 High Dose [2E11 vg], Untreated control	Week 96
Type of Statistical Test	Superiority	
Method	Other mixed model repeated measures	
Other LS Mean Difference	-3.0	
Standard Error of the mean	6.47	
90 % Confidence Interval 2-Sided	-13.8 to 7.8	

Change in Low luminance difference (LLD) letter count from Baseline at Weeks 12, 24, 36, 48, 72 and 96, via early treatment for diabetic retinopathy (ETDRS) chart - part 1

Description	LLD was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. The test was to be performed after BCVA testing, prior to pupil dilation, and distance refraction was to be carried out before Low Luminance Visual Acuity (LLVA) was measured. LLVA was to be measured by placing a 2.0-log-unit neutral density filter over the front of each eye and having the subject read the normally illuminated ETDRS chart. The LLD was calculated as the difference between BCVA and LLVA. Initially, letters were to be read at a distance of 4 metres from the chart. If <20 letters were read at 4 metres, testing at 1 metre should have been performed. LLD was to be reported as number of letters read correctly by the subject. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.
Time Frame	Baseline, Weeks 12, 24, 36, 48, 72 and 96

Analysis Population Description Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	9	12
Change in Low luminance difference (LLD) letter count from Baseline at Weeks 12, 24, 36, 48, 72 and 96, via early treatment for diabetic retinopathy (ETDRS) chart - part 1 (units: Letters read)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 1 - Week 12 (N=9,9,12)	2.0 ± 9.06	2.4 ± 22.49	-2.0 ± 7.21
Part 1 - Week 24 (n=9,9,10)	2.1 ± 8.40	2.9 ± 24.81	-2.9 ± 7.68
Part 1 - Week 36 (n=8,8,10)	2.3 ± 15.65	-7.5 ± 19.41	-4.0 ± 12.51
Part 1 - Week 48 (n=5,8,10)	3.0 ± 6.96	1.8 ± 26.25	-6.2 ± 19.99
Part 1 - Week 72 (n=5,8,10)	4.4 ± 7.57	3.1 ± 32.24	-6.6 ± 21.15
Part 1 - Week 96 (n=6,8,6)	5.2 ± 8.47	1.5 ± 29.17	-10.5 ± 27.41

Change in Low luminance difference (LLD) letter count from Baseline at Weeks 12, 24, 36, and 48, via early treatment for diabetic retinopathy (ETDRS) chart - part 2

Description LLD was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. The test was to be performed after BCVA testing, prior to pupil dilation, and distance refraction was to be carried out before Low Luminance Visual Acuity (LLVA) was measured. LLVA was to be measured by placing a 2.0-log-unit neutral density filter over the front of each eye and having the subject read the normally illuminated ETDRS chart. The LLD was calculated as the difference between BCVA and LLVA. Initially, letters were to be read at a distance of 4 metres from the chart. If <20 letters were read at 4 metres, testing at 1 metre should have been performed. LLD was to be reported as number of letters read correctly by the subject. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

Time Frame Baseline, Weeks 12, 24, 36, and 48

Analysis Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

Population

Description

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	18	0	20
Change in Low luminance difference (LLD) letter count from Baseline at Weeks 12, 24, 36, and 48, via early treatment for diabetic retinopathy (ETDRS) chart - part 2 (units: Letters read)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 2 - Week 12 (N=18,0,20)	0.7 ± 10.83		-1.4 ± 11.76
Part 2 - Week 24 (n=17,0,10)	2.6 ± 9.98		-1.6 ± 20.13
Part 2 - Week 36 (n=14,0,0)	4.6 ± 11.77		
Part 2 - Week 48 (n=5,0,0)	-2.8 ± 4.32		

Change from Baseline at Weeks 24, 36, 48, 72 and 96 in Reading performance, measured as the maximum reading speed (words per minute), as assessed by Minnesota low-vision reading test (MNRead) chart - part 1

Description The maximum reading speed (MRS) represents the highest reading speed an individual can achieve when print size is not a limiting factor. Essentially, it measures how quickly a person can read text when the print is large enough to be easily readable. A higher count represents better visual functioning.

Time Frame Baseline, Weeks 24, 36, 48, 72 and 96

Analysis Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.
Population
Description

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	8	9
Change from Baseline at Weeks 24, 36, 48, 72 and 96 in Reading performance, measured as the maximum reading speed (words per minute), as assessed by Minnesota low-vision reading test (MNRead) chart - part 1 (units: Words read per minute)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 1 - Week 24 (n=9,8,9)	20.384 ± 74.7769	-36.154 ± 40.3322	-7.837 ± 21.8918
Part 1 - Week 36 (n=7,7,8)	-15.048 ± 33.0479	-34.653 ± 27.2693	-15.245 ± 22.0983
Part 1 - Week 48 (n=4,7,9)	10.397 ± 11.8698	-36.285 ± 40.0938	-6.837 ± 31.6162
Part 1 - Week 72 (n=5,7,9)	-20.796 ± 42.2571	-44.913 ± 46.7594	-15.429 ± 30.1012
Part 1 - Week 96 (n=6,5,5)	10.802 ± 32.1161	-32.266 ± 36.9172	-21.602 ± 26.0643

Change from Baseline at Weeks 24, 36 and 48 in Reading performance, measured as the maximum reading speed (words per minute), as assessed by Minnesota low-vision reading test (MNRead) chart - part 2

Description A higher count represents better visual functioning.
Time Frame Baseline, Weeks 24, 36 and 48
Analysis Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.
Population
Description

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	16	0	10
Change from Baseline at Weeks 24, 36 and 48 in Reading performance, measured as the maximum reading speed (words per minute), as assessed by Minnesota low-vision reading test (MNRead) chart - part 2 (units: Words read per minute)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 2 - Week 24 (n=16,0,10)	15.581 ± 78.2848		-30.707 ± 27.3225
Part 2 - Week 36 (n=14,0,0)	9.812 ± 94.4255		
Part 2 - Week 48 (n=5,0,0)	-28.111 ± 38.6209		

Change from Baseline at Weeks 24, 36, 48, 72 and 96 in Functional reading independence (FRI) index - part 1

Description	The FRI index is a patient-reported outcome measure developed specifically for use in GA patients. The FRI index evaluates the level of independence subjects have in performing everyday activities that require reading, such as writing a cheque or reading a prescription. Scores derived from the index range from 1 (unable to do) to 4 (total independence). A higher score represents better visual functioning.
Time Frame	Baseline, Weeks 24, 36, 48, 72 and 96
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

GT005 Low Dose [2E10 vg] GT005 High Dose [2E11 vg] Untreated control

Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	8	10
Change from Baseline at Weeks 24, 36, 48, 72 and 96 in Functional reading independence (FRI) index - part 1 (units: Scores on a scale)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 1 - Week 24 (n=9,8,10)	0.7 ± 3.57	-1.3 ± 2.55	-0.3 ± 4.06
Part 1 - Week 36 (n=8,5,10)	-1.0 ± 4.24	2.6 ± 4.10	-0.6 ± 4.72
Part 1 - Week 48 (n=6,7,10)	0.5 ± 2.43	-0.1 ± 7.69	-3.4 ± 4.38
Part 1 - Week 72 (n=5,7,10)	-3.8 ± 4.60	0.4 ± 3.41	-1.3 ± 4.35
Part 1 - Week 96 (n=6,6,7)	-2.7 ± 5.79	-2.0 ± 3.29	-0.7 ± 5.53

Change from Baseline at Weeks 24, 36 and 48 in Functional reading independence (FRI) index - part 2

Description	The FRI index is a patient-reported outcome measure developed specifically for use in GA patients. The FRI index evaluates the level of independence subjects have in performing everyday activities that require reading, such as writing a cheque or reading a prescription. Scores derived from the index range from 1 (unable to do) to 4 (total independence). A higher score represents better visual functioning.
Time Frame	Baseline, Weeks 24, 36 and 48
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	17	0	9

Change from Baseline at Weeks 24, 36 and 48 in Functional reading independence (FRI) index - part 2
(units: Scores on a scale)

	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 2 - Week 24 (n=17,0,9)	-0.4 ± 2.83		0.4 ± 6.86
Part 2 - Week 36 (n=14,0,0)	-1.7 ± 3.83		
Part 2 - Week 48 (n=5,0,0)	0.4 ± 5.13		

Change From Baseline at Weeks 24, 36, 48, 72 and 96 in Patient Reported Outcomes (Visual Function Questionnaire-25) - Composite Score - Part 1

Description	The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains. The NEI 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. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. A composite score is derived based on the average of the 11 subscales.		
Time Frame	Baseline, Weeks 24, 36, 48, 72 and 96		
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.		

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	9	9	10
Change From Baseline at Weeks 24, 36, 48, 72 and 96 in Patient Reported Outcomes (Visual Function Questionnaire-25) - Composite Score - Part 1 (units: Scores on a Scale)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 1 - Week 24 (n=9,9,10)	-2.312 ± 5.7079	-3.755 ± 7.4470	-7.304 ± 12.5136

Part 1 - Week 36 (n=8,6,10)	-4.400 ± 11.1307	1.960 ± 9.0113	-4.706 ± 11.8617
Part 1 - Week 48 (n=6,8,10)	-6.439 ± 24.2128	-6.810 ± 11.5980	-4.091 ± 15.3598
Part 1 - Week 72 (n=5,8,10)	-8.698 ± 22.1289	-3.332 ± 8.1470	-3.826 ± 11.0029
Part 1 - Week 96 (n=6,7,7)	-10.352 ± 23.9470	0.171 ± 11.3543	-10.700 ± 11.6900

Change From Baseline at Weeks 24, 36, 48, 72 and 96 in Patient Reported Outcomes (Visual Function Questionnaire-25) - Composite Score - Part 2

Description	The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains. The NEI 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. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. A composite score is derived based on the average of the 11 subscales.
Time Frame	Baseline, Weeks 24, 36, 48, 72 and 96
Analysis Population Description	Full Analysis Set - for randomized participants with a valid measurement without a protocol deviation with impact.

	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Untreated control
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High Dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.
Number of Participants Analyzed [units: participants]	17	0	8
Change From Baseline at Weeks 24, 36, 48, 72 and 96 in Patient Reported Outcomes (Visual Function Questionnaire-25) - Composite Score - Part 2 (units: Scores on a Scale)	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation
Part 2 - Week 24 (n=17,0,8)	-4.034 ± 6.8881		-3.070 ± 7.4251
Part 2 - Week 36 (n=14,0,0)	-2.733 ± 7.9219		

Part 2 - Week 48 (n=5,0,0)

-0.530 ± 6.9722

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events are reported from randomization up to end of study, for a maximum timeframe of approximately 96 weeks.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	GT005 Low Dose [2E10 vg] N = 52	GT005 High dose [2E11 vg] N = 9	Untreated control N = 37	Overall N = 98
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.	Overall

Total Number Affected	3	0	2	5
Total Number At Risk	52	9	37	98

Serious Adverse Events

Time Frame	Adverse events are reported from randomization up to end of study, for a maximum timeframe of approximately 96 weeks.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

	GT005 Low Dose [2E10 vg] N = 52	GT005 High dose [2E11 vg] N = 9	Untreated control N = 37	Overall N = 98
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.	Overall
Total # Affected by any Serious Adverse Event	5	2	4	11
Total # at Risk by any Serious Adverse Event	52	9	37	98
Eye disorders				
Visual acuity reduced - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Infections and infestations

Cellulitis	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Gastroenteritis	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Pneumonia	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Staphylococcal infection	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Injury, poisoning and procedural complications				
Fall	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Hip fracture	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Rib fracture	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast cancer metastatic	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Hepatic cancer	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Lung adenocarcinoma stage IV	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Lung neoplasm malignant	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Nervous system disorders				
Amyotrophic lateral sclerosis	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Cerebrovascular accident	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Encephalopathy	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Sciatica	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Seizure	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Respiratory, thoracic and mediastinal disorders				
Choking	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Hypoxia	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)

Pleural effusion	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Pneumothorax	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events are reported from randomization up to end of study, for a maximum timeframe of approximately 96 weeks.
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 0%

	GT005 Low Dose [2E10 vg] N = 52	GT005 High dose [2E11 vg] N = 9	Untreated control N = 37	Overall N = 98
Arm/Group Description	GT005 Low Dose [2E10 vg]	GT005 High dose [2E11 vg]	Subjects allocated to the untreated control group did not receive any treatment.	Overall
Total # Affected by any Other Adverse Event	19	9	16	44
Total # at Risk by any Other Adverse Event	52	9	37	98

Blood and lymphatic system disorders

Anaemia	0 (0.00%)	1 (11.11%)	1 (2.70%)	2 (2.04%)
Hypochromic anaemia	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Cardiac disorders

Cardiomyopathy	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Coronary artery disease	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Ear and labyrinth disorders

Vertigo	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
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Eye disorders

Anterior chamber cell - Study eye	1 (1.92%)	1 (11.11%)	0 (0.00%)	2 (2.04%)
Anterior chamber flare - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Blepharitis - Fellow eye	2 (3.85%)	0 (0.00%)	0 (0.00%)	2 (2.04%)
Blepharitis - Study eye	2 (3.85%)	0 (0.00%)	0 (0.00%)	2 (2.04%)
Cataract - Fellow eye	0 (0.00%)	1 (11.11%)	2 (5.41%)	3 (3.06%)
Cataract - Study eye	3 (5.77%)	2 (22.22%)	1 (2.70%)	6 (6.12%)
Cataract nuclear - Study eye	2 (3.85%)	1 (11.11%)	0 (0.00%)	3 (3.06%)
Choroidal detachment - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Choroidal neovascularisation - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Conjunctival haemorrhage - Study eye	6 (11.54%)	1 (11.11%)	0 (0.00%)	7 (7.14%)
Conjunctival hyperaemia - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Conjunctivitis allergic - Fellow eye	1 (1.92%)	1 (11.11%)	0 (0.00%)	2 (2.04%)
Conjunctivitis allergic - Study eye	1 (1.92%)	1 (11.11%)	0 (0.00%)	2 (2.04%)
Dry eye - Fellow eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Dry eye - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Eye pain - Study eye	1 (1.92%)	2 (22.22%)	0 (0.00%)	3 (3.06%)
Eye pruritus - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Eye pruritus - Study eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Hypotony maculopathy - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Iridocyclitis - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Iritis - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Keratitis - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Lacrimation increased - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Macular hole - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Meibomian gland dysfunction - Fellow eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Meibomian gland dysfunction - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Metamorphopsia - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Ocular hypertension - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Open angle glaucoma - Fellow eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Open angle glaucoma - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Photophobia - Study eye	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Photopsia - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Photopsia - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Posterior capsule opacification - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Posterior capsule opacification - Study eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Punctate keratitis - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Retinal degeneration - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Retinal depigmentation - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Retinal haemorrhage - Fellow eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Retinal haemorrhage - Study eye	2 (3.85%)	1 (11.11%)	0 (0.00%)	3 (3.06%)
Retinal oedema - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)

Retinal pigmentation - Study eye	3 (5.77%)	6 (66.67%)	0 (0.00%)	9 (9.18%)
Retinal tear - Fellow eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Visual impairment - Fellow eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Visual impairment - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Visual snow syndrome - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Vitreous detachment - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Vitreous floaters - Fellow eye	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Vitreous floaters - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Vitreous haemorrhage - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Gastrointestinal disorders				
Abdominal pain upper	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Constipation	0 (0.00%)	0 (0.00%)	2 (5.41%)	2 (2.04%)
Diverticulum intestinal	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Dysphagia	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Hiatus hernia	0 (0.00%)	0 (0.00%)	2 (5.41%)	2 (2.04%)
Inguinal hernia	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Loose tooth	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Oesophageal achalasia	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Umbilical hernia	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
General disorders and administration site conditions				
Asthenia	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Drug intolerance	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Infections and infestations				
Bronchitis	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)

COVID-19	3 (5.77%)	2 (22.22%)	1 (2.70%)	6 (6.12%)
Cystitis	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Ear infection	1 (1.92%)	1 (11.11%)	0 (0.00%)	2 (2.04%)
Herpes zoster	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Sinusitis	0 (0.00%)	1 (11.11%)	1 (2.70%)	2 (2.04%)
Injury, poisoning and procedural complications				
Contusion	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Fall	1 (1.92%)	1 (11.11%)	1 (2.70%)	3 (3.06%)
Hand fracture	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Joint dislocation	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Ligament sprain	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Lower limb fracture	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Lumbar vertebral fracture	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Meniscus injury	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Muscle strain	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Post procedural discomfort - Study eye	2 (3.85%)	0 (0.00%)	0 (0.00%)	2 (2.04%)
Procedural pain - Study eye	1 (1.92%)	1 (11.11%)	0 (0.00%)	2 (2.04%)
Skin abrasion	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Skin laceration	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Suture related complication - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Tendon rupture	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Upper limb fracture	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Investigations				
Blood potassium decreased	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Blood pressure decreased	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)

Blood pressure increased	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
C-reactive protein increased	1 (1.92%)	0 (0.00%)	1 (2.70%)	2 (2.04%)
Intraocular pressure increased - Study eye	4 (7.69%)	3 (33.33%)	0 (0.00%)	7 (7.14%)
Metabolism and nutrition disorders				
Dyslipidaemia	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Obesity	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Vitamin D deficiency	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Musculoskeletal and connective tissue disorders				
Back pain	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Muscle contracture	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Osteoarthritis	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Pain in extremity	1 (1.92%)	1 (11.11%)	0 (0.00%)	2 (2.04%)
Plantar fasciitis	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Rotator cuff syndrome	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Spinal osteoarthritis	1 (1.92%)	0 (0.00%)	1 (2.70%)	2 (2.04%)
Temporomandibular joint syndrome	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast cancer recurrent	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Meningioma	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Nervous system disorders				
Carpal tunnel syndrome	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Cognitive disorder	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Dizziness	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Facial paralysis	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Headache	1 (1.92%)	0 (0.00%)	1 (2.70%)	2 (2.04%)
Hemiparesis	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Seizure	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Tension headache	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Transient ischaemic attack	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Psychiatric disorders				
Sleep disorder	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Renal and urinary disorders				
Dysuria	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Renal impairment	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Urethral haemorrhage	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Urethral polyp	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Reproductive system and breast disorders				
Vaginal haemorrhage	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Skin and subcutaneous tissue disorders				
Rosacea	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Telangiectasia - Fellow eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Telangiectasia - Study eye	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)
Urticaria	0 (0.00%)	1 (11.11%)	0 (0.00%)	1 (1.02%)
Vascular disorders				

Hypertension	0 (0.00%)	1 (11.11%)	1 (2.70%)	2 (2.04%)
Orthostatic hypotension	0 (0.00%)	0 (0.00%)	1 (2.70%)	1 (1.02%)
Peripheral ischaemia	1 (1.92%)	0 (0.00%)	0 (0.00%)	1 (1.02%)

Other Relevant Findings

Conclusion:

The study was terminated early following recommendation by Data Monitoring Committee (DMC) that overall benefit risk ratio did not support continuation of the current development program as planned.

Due to the study termination, the recruitment goal was not met as planned, with only approximately half of the intended sample size being randomized. Additionally, almost 80% of the randomized subjects dropped out of the study. Therefore, the results should be interpreted with caution.

The demographic and baseline disease characteristics of the study population were representative of the intended target population, albeit the race was predominantly White.

There was no decrease in the rate of Geographic atrophy (GA) progression in GT005-treated subjects. A gradual decline in Best corrected visual acuity (BCVA) was observed in all groups, as expected per GA natural history.

Safety assessments indicated that GT005 was generally safe and well tolerated in this study and the safety profile was in line with that observed to date in the clinical development program.

Date of Clinical Trial Report

17-Oct-2024