STATISTICAL ANALYSIS PLAN

Sponsor:	GenSight Biologics
Protocol No:	GS-LHON-CLIN-06 RESCUE and REVERSE Long-term Follow-up
Protocol Version No / Date:	Original Protocol: Version 1.0 / Date of Final Version: 21 July 2017 Protocol Amendment 1.0: Version 2.0 / Date of Final Version: 17 September 2018
Title:	Long-term Follow-up of *ND4* LHON Subjects Treated With GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials
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1. INTRODUCTION

Disease Review

Leber Hereditary Optic Neuropathy (LHON) is a rare, maternally inherited mitochondrial genetic disease, typically presenting as a non-syndromic optic neuropathy. Retinal ganglion cells (RGC), whose axons form the optic nerve, are the major cellular target affected by the resultant mitochondrial dysfunction. LHON was the first inherited human disease associated with point mutations in the mitochondrial DNA (mtDNA)[1] and it is considered the most common inherited genetic mitochondrial disorder.[2] LHON is a rare disease, and in Northern Europe, an estimated prevalence ranging from 1 in 30,000 to 1 in 50,000 has been reported.[3,4,5]

The clinical hallmark of LHON is central vision loss.[6] This is accompanied by dysfunction of color and contrast vision and central and cecocentral visual field defects and a final visual acuity of 20/200 or worse in 98% of eyes.[7,8] A prospective natural history study[9] reported LHON subjects with the G11778A *ND4* mutation. The primary outcome was the finding of no significant difference in the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity at 12, 24, or 36 months of follow-up compared to baseline at study entry. This finding was for the entire cohort as well as for the subgroups of patients who entered the study within 12 months of disease onset or after 12 months of disease onset. Improvement by ≥15 ETDRS letters occurred in 14.7% of total study eyes in 18% of study patients over the study period. Eighty-six percent of patients had eyes with stable acuities during study follow-up. Subjects entering the study after 36 months from disease onset showed no change or improvement of visual acuity over follow-up. The authors concluded that for the G11778A *ND4* mutation spontaneous natural recovery is partial and occurs on a very limited basis in a small percentage of subjects, and thus, gene therapy interventions can be measured for efficacy with a reasonable sample size.

Long-term Follow-up of the Benefits and Risks of Study Treatment

Investigational Medicinal Product

This long-term follow-up study is non-interventional, hence no investigational medicinal product (IMP) will be administered. GS010 was administered to subjects via standard intravitreal (IVT) injection in RESCUE and REVERSE. Please see the Phase III study protocols or the Investigator's Brochure for details on the IMP.

Generation of GS010 Safety Profile

For the safety profile of GS010 including expected adverse events, please refer to the current version of the Investigator's Brochure.

Statistical Analysis Plan

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under GenSight Biologics Protocol GS-LHON-CLIN-06.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed based on protocol Version 2.0 dated 17

September 2018 and eCRF Version 3.0 dated 13 June 2019. Any further changes to the protocol or CRF may necessitate updates to the SAP.

There are two interim and one final analyses planned for this study. The interim statistical analyses are planned after completion of Visit 3 (Year 3) and Visit 4 (Year 4), and the final analysis will be performed after completion of Visit 5 (Year 5).

The analysis of the secondary long-term efficacy analysis variable BCVA will be performed differently for the Federal Drug Administration (FDA) and European Medicine Agency (EMA). Details will be described in the respective sections.

2. STUDY OBJECTIVES

The study objectives are as follows:

Primary Objective:

- To assess the long-term safety of intravitreal GS010 administration up to 5 years post-treatment in subjects who were treated in the RESCUE or REVERSE studies.

Secondary Objectives:

- To assess the long-term efficacy of intravitreal GS010 administration up to 5 years post-treatment in subjects who were treated in the RESCUE or REVERSE studies.
- To assess the QoL in subjects who were treated with intravitreal GS010 in the RESCUE or REVERSE studies for up to 5 years post-treatment.

3. STUDY DESIGN

3.1 OVERALL DESIGN

This study is a multinational, multicenter, prospective, non-interventional, long-term follow-up clinical study of subjects previously treated with GS010 in either the RESCUE or REVERSE studies. Of the 7 investigational centers participating, 4 are located in Europe (1 each in France, Germany, Italy, and the United Kingdom) and 3 are located in the United States.

Subjects were enrolled in the long-term follow-up study when informed consent was provided and inclusion/exclusion criteria are met. Enrollment occurred during the Inclusion Period, which was during the RESCUE and REVERSE study Week 96/End-of-Study (EOS) Visit or anytime up to 1 day prior to the long-term follow-up study Visit 2 (Day 180). Preferably, the assessments required to be performed during the Inclusion Period were conducted at the RESCUE and REVERSE study Week 96/EOS visit; however, if the subject could not undergo all assessments at that time, the assessments may have been performed at a later date during the Inclusion Period, but no later than one day before the Year 2.5 visit (Day 180 post Week 96 (Visit 12 of CLIN-03)).

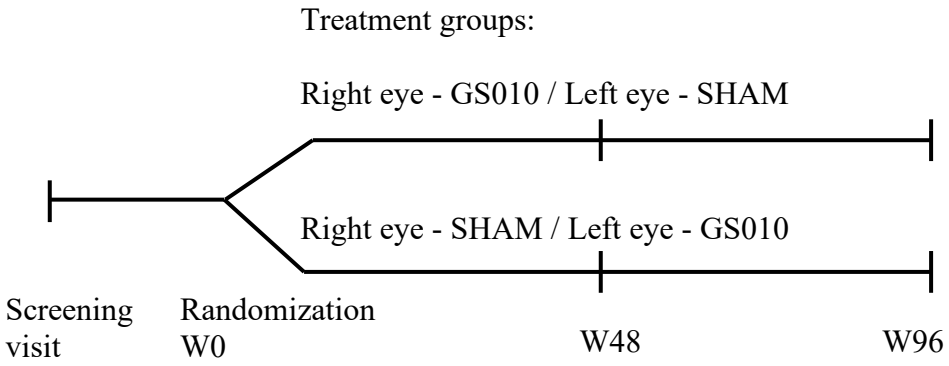
The study population was limited to the number of subjects treated in the RESCUE or REVERSE studies. The total length of the long-term follow-up study is 3 years and the total length of the subject follow-up from IMP administration will be 5 years.

The follow-up includes onsite assessments of safety, QoL, and efficacy as performed in the RESCUE and REVERSE studies. The study includes 5 follow-up study visits: at 2, 2.5, 3, 4, and 5 years post-treatment.

Statistical analysis of the data will include descriptive summaries of safety, QoL assessments, and statistical testing of efficacy endpoints.

In the RESCUE/REVERSE studies, both eyes received standard antiseptic preparation, were administered topical local ocular anesthetic agents, and had pupillary dilation. Administration of an intraocular pressure-lowering agent preceded treatment. GS010 was administered once during the study via a single intravitreal (IVT) injection. Sham IVT injection was performed by applying pressure to the eye at the location of a typical procedure using the blunt end of a syringe without a needle. The right eye of each subject was randomly allocated to receive either GS010 or sham treatment in a 1:1 allocation ratio. The fellow (left) eye received the treatment not allocated to the right eye. Therefore, each subject received GS010 in one eye and sham treatment in the fellow eye.

The schema of the study design of the RESCUE/REVERSE studies is given below:

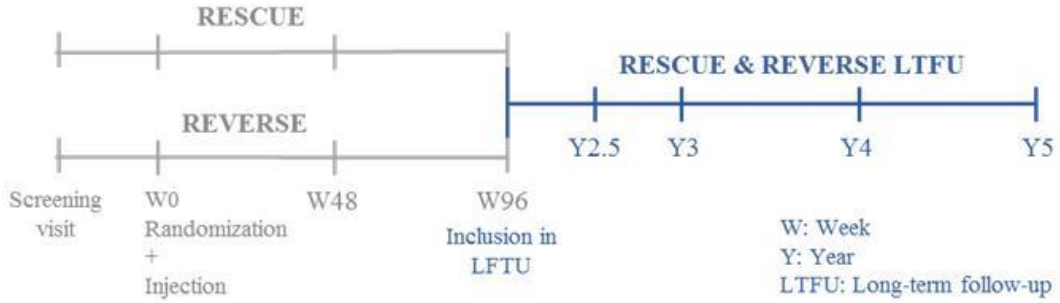


An algorithm with a testing hierarchy was employed to determine the best- and worst-seeing eye of each subject prior to randomization. The randomization was based on the right and left eye, because if the right eye was treated, the left eye would receive sham and vice versa, so the treatments were automatically balanced. However, the best- or worst-seeing eye at entry could have been a confounding factor, and it could not be excluded that the treatment effect would not be the same in the best and worst seeing-eye. In order to test this hypothesis with optimal power, an adaptive randomization technique called Efron's minimization[10] method was used to minimize the imbalance of treatment groups between the best-seeing eyes and worst-seeing eyes.

Masking was accomplished with sham injection of the fellow eye. Thus, treatment allocation was double-masked for both the subject and the investigation (follow-up) team, except the physician and medical team that performed the GS010 administration and sham injection and the first follow-up visit. Centralized analysis of the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity results, automated visual fields, SD-OCT, color vision and contrast sensitivity was performed by a masked central reading lab.

The schematic design of this long-term follow-up non-interventional study is given below:

Figure 1: Study Design Schematic of the Long-Term Follow-up of Subjects from the RESCUE and REVERSE Clinical Studies



Note: Inclusion into the long-term follow-up study will be allowed from Week 96 of the RESCUE/REVERSE studies up to 1 day prior to Year 2.5.

3.2 DURATION AND SCHEDULE OF STUDY PARTICIPATION

Study Duration

Total study follow-up is 3 years and the study will end with the last subject's last visit. The estimated total length of the subject follow-up is 5 years after the initial IMP administration.

Study Schedule

The follow-up study is divided into the following visits:

Visit 1: Inclusion Period (Year 2)

The Inclusion Period starts on the date of last visit (Week 96) of the RESCUE/REVERSE study and ends 1 day prior to Visit 2 (Year 2.5, Day 180 post Week 96 (Visit 12 of CLIN-03)) of the long-term follow-up study.

It is preferable for Visit 1 to be combined with Week 96/EOS visit of RESCUE/REVERSE study, but if not possible this can be a separate visit during the Inclusion Period. During this Period the informed consent is signed, eligibility criteria, adverse events (AEs)/ serious adverse events (SAEs) and concomitant medications (CMs) are reviewed and any other assessments needed that were not performed during the Week 96/EOS visit of RESCUE/REVERSE are completed.

Physical examinations including vital signs, electrocardiogram, laboratory assessments, quality of life, and ocular and vision assessments will also be done. A review of medical, surgical and prior medication history will also be performed.

Visit 2: Year 2.5 (± 4 Weeks) Post-treatment

During this visit, concomitant medications are reviewed, along with AEs and SAEs, and Ocular and Vision Assessments are carried out.

Visit 3: Year 3 (± 4 Weeks) Post-treatment

During this visit, assessments from Visit 2 are repeated and additional quality-of-life and Pelli-Robson contrast sensitivity assessments are carried out.

Visit 4: Year 4 (± 4 Weeks) Post-treatment

All assessments from Visit 3 are repeated during this visit.

Visit 5: Year 5 (± 4 Weeks) Post-treatment (EOS) or Early Termination Visit (ETV)

Assessments from Visit 4 are repeated. Additional physical examination including vital signs, electrocardiogram, and laboratory assessments, are performed.

Unscheduled Visit

Unscheduled visits can be performed anytime to assess or monitor AEs, or at the subject's or investigator's request. The date and reason for the unscheduled visit should be recorded in the source documents.

The study plan and assessments are shown in Protocol Section 8.2, Table 1: Schedule of Events of the protocol.

Table 1: Schedule of Events

Years post-treatment / Procedure	Inclusion Period	Long-term Follow-up Period			
	Year 2 (Week 96)[a]	Year 2.5 (± 4 weeks)	Year 3 (± 4 weeks)	Year 4 (± 4 weeks)	Year 5 EOS (± 4 weeks)[b]
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Informed consent	X				
Clinical Assessments/Procedures					
Review inclusion/exclusion criteria	X				
Medical history	X				
Physical examination including vital signs[c]	X				X
Electrocardiogram (12-lead)	X				X
Review concomitant medications	X	X	X	X	X
Adverse events/serious adverse events[d]	X	X	X	X	X
Laboratory Assessments					
Hematology/serum chemistry including liver function[e]	X				X
Quality of Life Assessments					
VFQ-25[f]	X		X	X	X
SF-36[f]	X		X	X	X
Ocular and Vision Assessments					
Slit-lamp examination[g]	X	X	X	X	X
Goldmann applanation tonometry for intraocular pressure[h]	X	X	X	X	X
Refraction for BCVA	X	X	X	X	X
Visual Acuity (ETDRS)	X	X	X	X	X
Humphrey™ visual field 30-2	X	X	X	X	X
Pelli-Robson contrast sensitivity[h]	X		X	X	X
SD-OCT	X	X	X	X	X
Color fundus photography	X	X	X	X	X

Abbreviations: BCVA, best-corrected visual acuity; EOS, End of Study; ETDRS, Early Treatment Diabetic Retinopathy Study; SD-OCT, spectral domain optical coherence tomography; SF-36v2, 36-item Short Form Health Survey; VFQ-25, Visual Function Questionnaire-25, version 2.

[a] The inclusion window will be from Week 96 visit up to 1 day prior to Visit 2, which will be approximately 180 days post W96/EOS.
[b] Subjects who discontinue participation in the long-term follow-up study prematurely (i.e., prior to Visit 5) will complete an EOS visit, including Visit 5 procedures.

[c] Examination includes general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities, and body weight and height. Vital signs include temperature, pulse rate, and systolic and diastolic blood pressure.
[d] Record in the eCRF any AE that is causally related to study medication and/or study procedure, any ocular AE (causally related or unrelated to study medication and/or study procedure), and any SAE (causally related or unrelated to study medication and/or study procedure).
[e] Refer to laboratory instruction manual for sample processing. Record in the eCRF any clinically significant abnormality, by parameter name and value, if deemed causally related to study medication and/or study procedure.
[f] Conduct after AE assessment and prior to visual acuity testing.
[g] Perform examination before and after pupil dilation.
[h] Perform examination before pupil dilation.

3.3 SAMPLE SIZE CONSIDERATIONS

A formal sample size calculation was not performed. The study population is limited to the number of subjects treated in the RESCUE and REVERSE studies.

3.4 RANDOMIZATION

This study does not include any randomization, as the treatment (GS010/sham) was randomized in the prior REVERSE/RESCUE studies. The right eye of each subject was randomly allocated to receive either GS010 or sham treatment in a 1:1 ratio. The fellow (left) eye received the treatment not allocated to the right eye.

3.5 MASKING

No investigational product will be administered during this long-term follow-up study. Unmasking procedures are not pertinent to this study as no study treatment/study procedures will be performed during the long-term follow-up.

4. STUDY ENDPOINTS, VARIABLES AND COVARIATES

4.1 PRIMARY ENDPOINT

The primary endpoint is adverse events (AEs) and serious adverse events (SAEs) (ocular or systemic) related to the Investigational Medical Product (IMP) or administration procedure, as judged by the investigator, and reported during the long-term follow-up visits (2, 2.5, 3, 4 and 5 years) from 96 weeks up to 5 years post-treatment.

4.2 SECONDARY SAFETY ENDPOINT

The secondary safety study endpoint is ocular or vision-related AEs reported during the post-treatment long-term follow-up visits from the period of 96 weeks up to 5 years.

4.3 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints are:

- Change in contrast sensitivity measured with the Pelli-Robson chart in all-, best-, and worst-eyes treated with GS010 IVT injection compared to all-, best-, and worst-eyes treated with sham IVT injection respectively to the follow-up study time points (2, 3, 4, and 5 years).
- Change in best-corrected visual acuity (BCVA) reported with Logarithm of the Minimal Angle of Resolution (LogMAR), change of parameters measured with Humphrey™ visual field (HVF) 30-2, and change of parameters measured with spectral-domain optical coherence tomography (SD-OCT) in all-, best- and worst-eyes treated with GS010 IVT injection compared to all-, best-, and worst-eyes treated with sham IVT injection respectively to each follow-up study time points (2, 2.5, 3, 4, and 5 years).
- Response status of eyes treated with GS010 IVT injection compared to eyes treated with sham IVT injection, including all-, best- and worst-eyes receiving GS010 or sham respectively, with responder eyes defined by:
    - An improvement of at least 15 ETDRS letters (equivalent to a decrease of at least 0.3 LogMAR) compared to baseline, or having a Snellen acuity equivalent better than 20/200.
    - Eyes that lose less than the 15 ETDRS letters (equivalent to an increase of less than 0.3 LogMAR) compared to baseline.
- Response status of subjects whose ETDRS scores of the treated eye are at least 15 letters better than the sham eye or whose treated eye has a LogMAR acuity of at least 0.3 LogMAR better than the sham eye at each long-term follow-up visit (2, 2.5, 3, 4, and 5 years).
- Visual improvement as measured by LogMAR to determine the difference in improvement (LogMAR) for all-GS010 eyes compared to all-sham eyes, for best-GS010 eyes compared

to best-sham eyes, and for worst-GS010 eyes compared to worst-sham eyes, with comparisons to baseline at each follow-up study time point (2, 2.5, 3, 4, and 5 years).

- Change of ganglion cell layer (GCL) volume and other parameters measured by SD-OCT for all-GS010 eyes compared to all-sham eyes, for best-GS010 eyes compared to best-sham eyes, and for worst-GS010 eyes compared with baseline at each follow-up study time point (2, 2.5, 3, 4, and 5 years).
- QoL as measured with the Visual Functioning Questionnaire 25 (VFQ-25), with change from baseline at each follow-up study time point (2, 2.5, 3, 4, and 5 years).
- 36-Item Short Form Health Survey, version 2 (SF-36-v2), with change from baseline at each follow-up study time point (2, 2.5, 3, 4, and 5 years).

4.4 PREDETERMINED COVARIATES AND PROGNOSTIC FACTORS

GCL thickness/volume and topographical maps, best or worst-seeing eye (eye status) as determined prior to randomization and duration of vision loss at the time of treatment could be significant prognostic factors for the treatment effect.

The baseline LogMAR will also be used as a covariate for analysis of change in LogMAR. Similarly, the baseline of the endpoint being analyzed will be used as the model's covariate.

The investigative site will not be included in the analysis as the number of subjects recruited per site will be very small. However, stratification by geographical area may be performed as a sensitivity analysis. Neighboring countries can be pooled to reach at least 9 subjects per geographical entity. All analysis will be performed using an alpha of 0.05 (two-sided test).

These covariates will be used in the analyses presented in Section 9.5 Efficacy Analysis.

5. DEFINITIONS

5.1 STUDY DAY

All study days on or after the treatment administration (from the prior RESCUE/REVERSE studies) will be calculated as date of assessment minus date of treatment administration + 1. Study days before the treatment administration will be calculated as date of assessment minus date of treatment administration. In case of missing or incomplete dates no study days will be calculated.

5.2 BASELINE

The baseline value is defined as the last non-missing value prior to the start time of treatment administration in the RESCUE/REVERSE studies (Week 0). If assessment and treatment administration occur on same day and time is not captured, it will be considered as baseline.

For OCT parameters baseline is defined as the last non-missing value prior to the start time of treatment administration in the RESCUE/REVERSE studies (Week 0).

5.3 CHANGE FROM BASELINE

The change from baseline value is defined as the value at a given time point minus the baseline value.

5.4 DERIVED VARIABLES

ETDRS Score and LogMAR (on chart and off chart)

- ETDRS score is calculated by the examiner and written on the source documents and entered in the eCRF.
- LogMAR (on chart and off chart) will all be derived in eCRF from the Snellen/decimal acuity.

I. 1 ETDRS line = 5 letters

II. 1 ETDRS line = 0.1 LogMAR

III. 0.1 LogMAR = 5 ETDRS letters

IV. 15 ETDRS letters = 0.3 LogMAR

V. A less positive/more negative LogMAR is an improvement of vision

VI. An increase in the number of ETDRS letters read is an improvement of vision

- On-Chart subjects: defined as being able to read at least 3 ETDRS letters on a single line on the ETDRS chart at either 4 or 1 meters
    a. Have an obtainable Snellen equivalent obtained directly from ETDRS chart

b. Each Snellen equivalent is assigned a LogMAR value. A Snellen score of 6/6, 20/20, indicating that an observer can resolve details as small as 1 minute of visual angle, corresponds to a LogMAR of 0, since the base-10 logarithm of 1 is 0. A Snellen score of 6/12, 20/40, indicating an observer can resolve details as small as 2 minutes of visual angle, corresponds to a LogMAR of 0.3, since the base-10 logarithm of 2 is near-approximately 0.3, and so on.

- Off-chart subjects: defined as a subject who cannot read at least 3 ETDRS letters on a single line of the ETDRS chart at 1 meter and thus have no Snellen equivalent obtainable from ETDRS chart
    a. These subjects are categorized as able to either count fingers (CF), detect hand motion (HM), detect light perception (LP), or are no-light perception (NLP).
    b. If there is no CF and HM and a subject's visual acuity is light perception, then a LogMAR value of 4 will be assigned. If a subject's visual acuity is no light perception, then a LogMAR value of 4.5 will be assigned.
    c. For those categorized as CF a LogMAR value of 2 will be assigned (Lange equivalence)
    d. For those categorized as HM a LogMAR value of 2.3 will be assigned (Lange equivalence).

LogCS

Contrast sensitivity was assessed using the Pelli-Robson chart for low vision, on a scale from zero to 2.5 LogCS. Subjects who could not read at least 2 out of the first 3 letters on the Pelli-Robson chart will be assigned the worst possible score (a LogCS of zero).

- LogCS is obtained based on which letter triplets the subject can read correctly on the chart, and the LogCS value is then entered in the eCRF.

Nadir of LogCS

Nadir of LogCS is defined for each eye of each subject as the worst LogCS observed from baseline to the visit of interest, including baseline and visit of interest values.

If contrast sensitivity is off-chart at any time point in the study, the first off-chart LogCS value will be considered to be the nadir, with the applied equivalence of LogCS 0.

BCVA and HVF

- Best-corrected visual acuity (BCVA), Humphrey Visual Field 30-2 (HVF) and Spectral Domain Optical Coherence Tomography (SD-OCT) will be assessed and then recorded on the eCRF.

Nadir of BCVA

The Nadir of BCVA is defined for each eye of each subject as the worst BCVA observed from baseline to the visit of interest, including baseline and visit of interest values. The first occurrence of this value will be considered as Nadir.

Responder Definitions

Eye Responder

- Definition 1: An improvement of at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to a decrease of at least 0.3 LogMAR) compared to baseline, or having a Snellen acuity equivalent better than 20/200 (equivalent to 1 LogMAR).
- Definition 2: Eyes that lose less than the 15 ETDRS letters (equivalent to an increase of less than 0.3 LogMAR) compared to baseline.

Subject Responder

- A subject will be considered a responder if the ETDRS score of the treated eye is at least 15 ETDRS letters better than the sham eye, or if the treated eye has a LogMAR acuity at least 0.3 LogMAR better than the sham eye, at a given visit (2, 2.5, 3, 4 and 5 years).

Vision Loss Duration at the Time of Treatment

- Vision loss duration in days will be based on the difference between the date of onset of vision loss of the first affected eye and baseline date (last BCVA non-missing value prior to the start time of treatment administration in the RESCUE/REVERSE studies).
- Vision loss duration will also be calculated for the second affected eye.

Treatment-Emergent Adverse Events (TEAE)

Treatment-emergent adverse events (TEAEs) are defined as AEs that started after study treatment administration in the prior RESCUE/REVERSE studies or that represent an exacerbation of a condition that is present at baseline after treatment administration. Worsening of visual acuity determined by the investigator to be due to progression of LHON will not be considered as an AE. Any AE with an unknown start date will be considered treatment-emergent if the event does not stop prior to study treatment administration. AEs with partial dates are described in Section 5.5.2.

Prior and Concomitant Treatment

Prior and Concomitant treatments will be coded using the current WHO Drug Dictionary (WHODD) version. For each medical entity, all Anatomical Therapeutic Chemical (ATC) codes will be assigned according to the therapeutic classes to which the treatment belongs. Coding of treatments is detailed in the Coding Guidelines.

Prior treatments will be defined as any treatments with start date and time prior to the study treatment administration date and time.

Concomitant treatments will be defined as any treatments ongoing at the start of study treatment administration or with a start date and time on or after the study treatment administration date and time. Treatments with partial dates will be dealt similarly as AEs with partial dates described in Section 5.5.2. If the start time is missing, then treatments will be assigned 'concomitant' based on start date of treatments only if it is on or after the treatment administration date.

Note that concomitant medication summaries will be provided for medications collected during the originating study (RESCUE or REVERSE), for the follow-up period of CLIN-06, and combined.

Visual Functioning Questionnaire-25

The VFQ-25 Questionnaire (Section 9.5.2 of the protocol) is a 25-item version of the 51-item National Eye Institute Visual Function Questionnaire. The VFQ-25 consists of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored from 0 to 5, so that a higher number represents better functioning. To score the questionnaire, each item is converted to a 0-100 scale. Items within each subscale are averaged to create 12 subscale scores. The subscale scores (excluding the general health rating question) are then averaged to calculate the composite score[11].

36-Item Short Form Health Survey, Version 2

The SF-36 Questionnaire (Section 9.5.1 of the protocol) is a generic, subject-reported outcome instrument used to assess QoL. The SF-36 is a 36-question instrument, which assesses 8 health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Each question has 5 answers scored 1 (unable to) to 5 (no difficulty). The scale score of each domain is calculated based on the summed score across items included in the domain and is rescaled to 0 to 100 with higher scores indicating better health states[12].

5.5 HANDLING OF MISSING DATA AND/OR INVALID DATA AND OUTLIERS

5.5.1 Efficacy

In case of missing data, the following rules will be applied as a primary imputation method applicable to all visits of interest (follow-up study time points 2, 2.5, 3, 4 and 5 years):

For all analysis timepoints, a review of the visits with available BCVA value will be done by GenSight to decide, for each patient, which visit will be used for this specific timepoint analysis. The document will be provided in excel format, and then imported in SAS in order for the statistician to perform the analysis (CLIN-06_DRM_Listings_V1.0_30JUN2022).

If Year-2 visit is not available at Clin06 inclusion, then "Follow-up Visit 12" (corresponding to Week 96) from Clin03A/Clin03B will be used.

After this affectation, in case of missing LogMAR value at a visit, LOCF will be applied with all analysed visits.

When a test result score/value for the Pelli-Robson Contrast test is missing at any visit for the reason that the subject was unable to perform because the vision was too poor, the following convention will be used: the worst possible score for the given test will be assigned as the value for that visit (i.e., 0 LogCS).

The imputation method of missing data used in each analysis will be specified in the TFLs in a footnote.

5.5.2 Safety

Missing/partial start date and missing/partial end date for all TEAEs will be imputed.

Missing/Partial Start Date for AEs

The following rules will be applied to missing or incomplete start dates when determining if an AE is treatment emergent. The rules will be applied first before determining the treatment emergent status and imputed dates will be treated as complete dates for this purpose. These rules are intended to lead to a conservative assessment of treatment emergence. The imputed dates are only used for determining treatment emergence and the recorded partial dates will be displayed in listings. The same rules will be applied for prior and concomitant medications as per Section 5.4.

If the year of onset of the AE is missing, then the AE is considered treatment emergent.

If the year of the AE onset date is complete, but the month and day of the onset of the AE are missing, then the following rules apply:

- If the year of the AE is the same as the year of the study treatment administration then the AE is considered treatment emergent, and the AE onset date will be set to the study treatment administration date.
- If the year of the AE onset date is after the year of study treatment administration, then the date is set to 01 January and the AE is considered treatment emergent.
- If the year of the AE onset date is before the year of study treatment administration date, then the AE is not treatment emergent.

If the year and month of the AE onset date are complete, but the day of the onset of the AE is missing, then the following rules apply:

- If the year and month of the AE onset date is the same as the year and month of the treatment administration date, then the AE is considered treatment emergent and the AE onset date will be set to the treatment administration date.
- If the year and the month of the AE onset date are complete, and the month of the AE onset date is after the month of the study treatment administration date, then the day of the AE

onset date will be set to the first day of the month. The AE will be assigned as treatment emergent.

- If the year and the month of the AE onset date are before the year and the month of treatment administration date, then the AE is not treatment emergent.

Missing/Partial End Date for AEs

If the end date is missing and the start date is on or after the date of treatment administration, then the AE is considered treatment emergent.

Missing/Partial Dates for Prior and Concomitant Treatments

Missing and partial dates of prior and concomitant treatments will be dealt similarly as partial dates for AEs.

If the year and month of the medication end date are complete and there is no day value, and the month of the medication end date is on or after the month of the long-term follow-up study start date, then the day of the medication end date will be set to the first day of the month. The medication will be assigned as prior or concomitant medication based on the imputed date.

All relevant prior medications will be recorded, including prescription and non-prescription medications, preparations and health and/or dietary supplements taken by the subject. Concomitant medications from the RESCUE and REVERSE studies will be recorded as prior medications, with respect to the long-term follow-up study. If the concomitant medication on the RESCUE and REVERSE prior studies are not ongoing at enrollment in CLIN-06, then they will be defined as prior to CLIN-06, if still ongoing they will be defined as concomitant for CLIN-06. In summary, a medication will be assigned to, 1, 2 or 3, of 3 time periods: prior to treatment, after treatment, but occurring during RESCUE or REVERSE, and after treatment, but occurring during CLIN-06. A medicine may be assigned to more than 1 of the 3 periods, if its use spans multiple periods.

Missing Severity or Relationship to Study Treatment/Study Procedure of an AE

If the intensity of an AE is missing, an intensity of "severe" will be imputed.

If the relationship to study treatment/study procedure is missing, a relationship of "probable" will be imputed.

Missing/Partial End Date for Other Safety Variables

For other safety variables a similar approach for missing end dates will be followed in the data derivation of the Analysis Data Model (ADaM) specifications.

The same approach will be undertaken for the imputation of missing/partial end dates related to prior and concomitant treatments.

Missing/Partial End Date for Vision Loss

Five patients from Rescue study have a missing vision loss onset date for one eye. Theses 5 eyes' date of vision loss will be imputed with the following values (based on the evolution of LogMAR values):

- Patient 120001 left eye (Sham) onset of vision loss on 29 August 2016
- Patient 120007 right eye (Sham) onset of vision loss on 02 September 2017
- Patient 140002 right eye (Treated) onset of vision loss on 10 June 2016
- Patient 140006 left eye (Sham) onset of vision loss on 20 March 2017
- Patient 150004 right eye (Treated) onset of vision loss on 25 August 2016

6. ANALYSIS SETS

6.1 SAFETY

The Safety Population is defined as those subjects who received study medication in RESCUE or REVERSE Phase III studies and consented to be enrolled in this long-term follow-up study. This population will be used as the population for all safety analyses.

6.2 MODIFIED INTENT-TO-TREAT

The Modified Intent-to-Treat (mITT) Population is defined as those subjects who received study medication in RESCUE or REVERSE Phase III studies, consented to be enrolled in this long-term follow-up study, and provide visual acuity data at Visit 2. This population will be used as the primary population for efficacy and QoL analyses. This population is identical to the Safety Population. Missing non-safety endpoints will be imputed with LOCF.

6.3 PER PROTOCOL

The Per Protocol (PP) Population is the subset of mITT who completed the follow-up study, and have data available at scheduled/unscheduled (within the allowable time window) visit. This population will be used as the for supportive efficacy and QoL analyses. Missing data will not be imputed.

6.4 ANALYSIS SUBSETS

- The Pediatric subset is defined as those subjects who received study medication (GS010 and sham treatment) who were less than 18 years old at the time of the Screening Visit in RESCUE or REVERSE Phase III studies. This population will be used for specific safety, efficacy and QoL analyses as deemed appropriate.
- Best eye and worst eye subsets of mITT and PP are based on the eye designation at baseline in RESCUE or REVERSE Phase III studies.
- On-chart LogMAR at baseline subsets are based on the baseline LogMAR in RESCUE or REVERSE Phase III studies.
- Subjects from the RESCUE Phase III study.
- Subjects from the REVERSE Phase III study.

7. INTERIM ANALYSES

Two interim analyses are planned at completion of Visit 3 (Year 3) and Visit 4 (Year 4), in addition to the final analysis at Year 5. The final results based on all time points will be included in the final Clinical Study Report (CSR).

No Data Monitoring Committee (DMC) will be assembled for evaluation of results in this long-term follow-up study.

8. STATISTICAL METHODS

All analyses will be performed on SAS Version 9.4 or higher.

Unless otherwise noted, categorical and binary variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum. Change from baseline or from nadir will also by summarized by a 95% confidence interval (CI).

Least square means, 95% CIs, and p-values will be reported from ANCOVA models. Estimated proportions with 95% CIs will be provided for Generalized Estimating Equation (GEE) models and for logistic regression models for responder endpoints. ANCOVA models will be run on all continuous endpoints, logistic regression for all subject responder endpoints, and GEE models for all eye responder endpoints.

Rounding rules are generally as follows:

- If the original variable has x decimal places, then minimum and maximum with be reported with x decimal places; mean, median, Q1, Q3, SD and CIs will be reported with x+1 decimal places.
- P-values will be reported with four decimal places.

Summary TFLs will display standard headers containing the sponsor name (“GenSight Biologics”) as well as a standard footer containing the name of the program used to generate the display, its path, and a date stamp. Headers, footers, titles, and column headers for tables will be repeated on every page of each display; pages will be numbered “Page x of y.” Visit labels in tables and figures will show visit name. Summary TFLs containing no applicable data will display a line reading, “No applicable data were reported” or similar wording. Dates and times will be presented using SAS DATE9. and SAS TIME5. formats.

8.1 SUBJECT DISPOSITION

The number and percentage of subjects, who were enrolled and who completed the study will be presented, together with the number and percentage of subjects who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal. These data will also be listed according to the eCRF. The number and percentage of subjects in the Safety, mITT, PP, and Pediatric Populations will also be presented.

Number of subjects who missed visits and the subjects who attended a particular visit will be presented. In addition, number of missing data for visual acuity and important SD-OCT parameters will also be summarized.

8.2 PROTOCOL DEVIATIONS AND VIOLATIONS

All protocol deviations will be listed. The decision regarding the major protocol deviations will be taken during the data review meeting.

8.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (gender, age, weight, height) will be summarized using descriptive statistics. Qualitative variables (gender) will be summarized using frequencies while quantitative variables (age, weight, height) will be summarized using mean, SD, median, Q1, Q3, minimum and maximum. These baseline demographic data will be imported from the RESCUE or REVERSE clinical database into the long-term follow-up clinical database.

Demographic and baseline characteristics will be summarized for the Safety Population. The analysis will be presented for RESCUE and REVERSE studies separately and pooled.

These data will also be listed based on the data listed in the eCRF.

Medical and surgical history data will be summarized by using counts and percentages and will be presented by system organ class and preferred term.

8.4 TREATMENTS

8.4.1 Extent of Study Drug Exposure

This study is the follow up of RESCUE/REVERSE studies where a single IVT injection was administered into the randomized eye and a single sham IVT injection in fellow eye on same day. Therefore, no summary table will be produced for the exposure data.

8.4.2 Concomitant Treatments

Prior and concomitant treatments will be coded using the World Health Organization dictionary (WHO Drug Dictionary current version). For each medical entity all Anatomical Therapeutic-Chemical (ATC) codes will be assigned according to the therapeutic classes to which the treatment belongs. Coding of treatments is detailed in the Coding Guidelines.

Prior and concomitant treatments will be summarized for the Safety Population by number and percentage of subjects of WHO Drug Dictionary ATC levels (ATC1, ATC2) and preferred term (PT). All prior and concomitant treatment data will be listed.

Concomitant medications from the RESCUE and REVERSE studies will be recorded as concomitant for those studies and those from the long-term follow-up study will be summarized separately. A combined summary of all concomitant medications will also be provided. Medications that span the original as well as the long-term follow-up study will be counted in both.

8.5 EFFICACY ANALYSES

All efficacy analysis will be conducted on the mITT Population, the PP Population, and additionally in subset populations as appropriate. All summaries will be performed on RESCUE separately, REVERSE separately, and on RESCUE and REVERSE combined.

8.5.1 Primary Efficacy Variable

Not applicable for this study.

8.5.2 Secondary Efficacy Variables

8.5.2.1 Pelli-Robson Contrast Sensitivity

Eye Level

Contrast Sensitivity will be summarized at each follow-up visit (Years 2, 3, 4, and 5), along with change from baseline to each follow-up visit.

This summary will be done comparing all-GS010 eyes to all-sham eyes.

These summary tables will be reproduced for eyes with on-chart LogCS at baseline, with off-chart LogCS at baseline (equivalence LogCS 0), and for all eyes.

The change of LogCS from baseline to the visit of interest will be compared between all-GS010 treated eyes and all-Sham treated eyes.

At each visit of interest, the following analyses related to Nadir LogCS will be performed:

- The change from Nadir LogCS will be calculated for each eye of each subject and will be expressed in LogCS.
- The time to Nadir LogCS will be calculated for each eye of each subject and will be expressed in Weeks.
- The mean LogCS change from Nadir will be assessed for all eyes, all GS010 eyes and all-Sham eyes.
- The mean time to Nadir LogCS will be assessed for all eyes, all GS010 eyes and all-Sham eyes.

Subject Level

At subject level, the best outcome (change from Baseline or change from Nadir) observed in either eye will be considered. The following summaries will be presented:

- The change of LogCS from baseline to the visit of interest
- The change of LogCS from Nadir to the visit of interest

8.5.2.2 LogMAR

Eye Level

Mean LogMAR BCVA will be summarized at each follow-up visit (Years 2, 2.5, 3, 4 and 5), along with mean change from baseline to each follow-up visit.

This summary comparing all-GS010 eyes to all-sham eyes will be repeated by comparing best-GS010 eyes to best-sham eyes and worst-GS010 eyes to worst-sham eyes.

These summary tables will be reproduced for those eyes with on-chart BCVA at baseline.

The curves of change from baseline at each time point for treated and sham eyes will be produced, with both sham and treated curves on same graph

The curves of absolute BCVA values at each time point for treated and sham eyes will be produced with both sham and treated curves on same graph.

LogMAR BCVA will be analyzed by using two approaches:

For the EMA, the change of LogMAR from baseline to the visit of interest will be compared between all-GS010 treated eyes and all-Sham treated eyes using a mixed-effects analysis of covariance (ANCOVA), with baseline LogMAR as a covariate, and subject and eyes of the subject as random factors.

The FDA has recommended comparing GS010 vs Sham in the Best-seeing eyes as a primary analysis. Therefore, change of LogMAR from baseline to the visit of interest will be compared between Best-GS010 treated eyes and Best-Sham treated eyes for the FDA. ANCOVA will be used for this analysis.

The EMA analysis is based on intra-subject comparison of change of LogMAR from baseline to the visit of interest. For FDA, the analysis is based on inter-subject comparison of change of LogMAR from baseline.

For eyes with on-chart BCVA at baseline, the change of LogMAR from baseline to the visit of interest will be analyzed between GS010-treated eyes and Sham-treated eyes.

At each visit of interest, the following analyses related to Nadir BCVA will be performed:

- The change from Nadir BCVA will be calculated for each eye of each subject and will be expressed in LogMAR.
- The time to Nadir BCVA will be calculated for each eye of each subject and will be expressed in Weeks.
- The mean LogMAR change from Nadir will be assessed for all eyes, all GS010 eyes and all sham eyes.
- The mean time to Nadir BCVA will be assessed for all eyes, all GS010 eyes and all sham eyes.

Subject Level

At subject level, the best outcome observed in either eye will be considered. The following summaries will be presented:

- The change of LogMAR BCVA from baseline to the visit of interest
- The change of LogMAR BCVA from nadir to the visit of interest

Analysis for European Medicines Agency (EMA)

The primary analysis will be performed on the mITT Population. The change from baseline to each follow-up visit in the LogMAR acuity will be the response. The change from baseline of all-GS010 eyes will be compared to the change from baseline of all-sham eyes applying a mixed-effects ANCOVA model using the following terms (or covariate) in the model:

- Subject as a random factor.
- The baseline LogMAR as a covariate.
- Treatment as a fixed effect.

The null and alternative hypotheses for the EMA LogMAR analysis are:

H_0: $\mu_{\text{All-GS010}} = \mu_{\text{All-Sham}}$

H_1: $\mu_{\text{All-GS010}} \neq \mu_{\text{All-Sham}}$,

where μ presents the mean change from baseline to the visit of interest in LogMAR and "All" represents all eyes treated with GS010 or Sham.

The investigative site will not be included in the analysis as the number of subjects recruited per site will be very small. However, stratification by geographical area may be performed as a sensitivity analysis. Neighboring countries can be pooled to reach at least 9 subjects per geographical entity. The analysis will be performed using an alpha of 0.05 (two-sided test).

An additional model may add the treatment by geographical interaction (geographical areas: USA and Europe) to investigate the generalizability of the treatment effect. The following model diagnostics may be checked: normality of error terms, independence of error terms, independence of the covariate and treatment effect, and homogeneity of error variances.

Analysis for Food and Drug Administration

The primary analysis will be based on the mITT Population. The change from baseline of the best-GS010 treated eyes will be compared to the change from baseline of the best-sham eyes (inter-subject comparison) using an ANCOVA with baseline LogMAR as covariate. The analysis will be performed using an alpha of 0.05 (two-sided test). The statistical significance in favor of the best-GS010 treated eyes against the best-sham eyes will show evidence of the advantage of using GS010 for halting visual acuity loss or improving visual acuity in subjects with LHON. The difference in the mean change from baseline (adjusted mean difference) between the two treatment groups and associated 95% confidence interval will be reported.

The null and alternative hypotheses for the FDA LogMAR analysis are:

H_0: $\mu_{\text{Best-GS010}} = \mu_{\text{Best-Sham}}$

H_1: $\mu_{\text{Best-GS010}} \neq \mu_{\text{Best-Sham}}$,

where μ presents the mean change from baseline to the visit of interest in LogMAR and "Best" represents the best-seeing eyes.

The following model diagnostics may be checked: linearity of regression, normality of error terms, independence of error terms, independence of the covariate and treatment effect, homogeneity of error variances, homogeneity of regression slopes.

8.5.2.3 Parameters Measured with SD-OCT

Parameters of High Resolution SD-OCT

A central reading center will perform quality control, analysis and interpretation of all SD-OCT data. The following parameters will be summarized:

a. Ganglion Cell Layer (GCL) macular volume
b. Retinal nerve fiber layer (RNFL) thickness
    i. Average (360 degrees)
    ii. Temporal quadrant
    iii. Papillomacular bundle (PMB)
c. ETDRS Macular Volume

SD-OCT parameters will be summarized at each follow-up visit (Years 2, 2.5, 3, 4 and 5), along with change from baseline to each follow-up visit. This summary will be repeated by comparing all-GS010 eyes to all-sham eyes.

The change of GCL volume and other parameters measured by SD-OCT (e.g., RNFL average thickness, RNFL Temporal Quadrant thickness, RNFL PMB thickness, ETDRS Macular Volume) from baseline to each follow-up visit (Years 2, 2.5, 2, 4 and 5) will be analyzed using a mixed-effects ANCOVA, including the subject as a random factor, the treatment and the baseline GCL volume (if available) as covariates in the model. The analysis will be performed using an alpha of 0.05 (two-sided test). The difference in the mean change from baseline (adjusted mean difference) to each follow-up visit between the two treatment groups (all-GS010 vs all-sham) and associated 95% confidence interval will be reported.

Additional Analyses and graphic presentations

A bar chart representation of GCL macular volumes at baseline will be produced (y axis: percentage; x axis: distribution of GCL macular volume values in mm^3). A bar chart of disease duration by GCL macular volume at baseline will be produced (y axis: percentage; x axis: 4 groups of GCL macular volume [≤0.5;]0.5;0.6];]0.6;0.7]; >0.7] combined with distribution of time from vision loss).

We will perform regression analyses of GCL macular volume at baseline in function of BCVA at baseline with calculation of R^2 and slope p value (using univariate Student test), and production of corresponding graphs. These analyses will be performed on all eyes, GS010 eyes and sham eyes.

LOESS model curves for GCL macular volume over time for all eyes, GS010 eyes and sham eyes, will be produced. Smoothing parameters selection will be based on the corrected Akaike's Information Criterion AICC (SAS default method with values from 0.3 to 0.6) and specified for each LOESS curve.

Subgroups analyses will be performed to investigate the relationship between OCT parameters and final BCVA at 5 years post treatment.

4 subgroups of eyes will be defined based on final LogMAR ranges:

- Group 1: ≤1 LogMAR
- Group 2: >1 to ≤1.3 LogMAR
- Group 3: >1.3 to ≤1.6 LogMAR
- Group 4: > 1.6 LogMAR

GCL macular volume absolute change from baseline by BCVA subgroups at 5 years post treatment will be provided. A corresponding bar chart will be produced (y axis: mean of GCL macular volume absolute change and x axis: subgroups of final BCVA).

A multivariate analysis on all eyes will be performed, in order to evaluate covariates impacting the final BCVA value, with the final LogMAR value as dependent variable. The covariates will be eye treatment status, GCL macular volume at baseline, GCL macular volume relative change from baseline (%) and LogMAR value at baseline. The same multivariate analysis will be performed for GS010 eyes and sham eyes separately.

We will perform regression analyses of GCL macular volume at final assessment in function of BCVA at final assessment with calculation of R^2 and slope p value (using univariate t-test from SAS proc mixed), and production of corresponding graphs. These analyses will be performed on all eyes, GS010 eyes and sham eyes.

We will perform regression analyses of BCVA at last assessment in function of GCL macular volume baseline value, with calculation of R^2 and slope p value (using univariate t-test from SAS proc mixed), and production of corresponding graphs. These analyses will be performed on all eyes, GS010 eyes and sham eyes.

8.5.2.4 Responder Analysis

Eye Level – Eye Responder

LogMAR BCVA

Eye Responder analyses will be carried out at the visit of interest for the following definitions:

- Eyes with an improvement of at least 15 ETDRS letters (equivalent to a decrease of at least 0.3 LogMAR) compared to baseline, or having a Snellen acuity equivalent better than 20/200.
- Eyes that lost less than 15 ETDRS letters (equivalent to an increase of less than 0.3 LogMAR) compared to baseline.
- For eyes with on-chart BCVA at baseline, an improvement of at least 15 ETDRS letters (equivalent to a decrease of at least 0.3 LogMAR) compared to baseline.

Number and percentage of responders and non-responders will be summarized at all the follow-up visits (Years 2, 2.5, 3, 4 and 5). A GEE model will be used for comparisons of all-GS010 eyes against all-sham eyes to each of the follow-up visits.

The analysis will also be performed to compare best-GS010 eyes against best-Sham eyes and worst-GS010 eyes against worst-Sham eyes, giving number and percentage of responders and non-responders. However, instead of using a GEE model, a logistic regression will be used for these analyses, as the data are independent.

The following responders analyses will be performed on all eyes, all GS010 eyes and all sham eyes.

- Eyes with Clinically Relevant Recovery (CRR) from baseline at visit of interest, defined as:
  - For eyes on-chart at baseline, an improvement of at least -0.2 LogMAR from baseline at visit of interest,
  - For eyes off-chart at baseline, eyes which became on-chart (LogMAR ≤1.6) at visit of interest.

- Eyes with Clinically Relevant Recovery (CRR) from Nadir at visit of interest, defined as:
  - For eyes on-chart at Nadir, an improvement of at least -0.2 LogMAR from Nadir at visit of interest,
  - For eyes off-chart at Nadir, eyes which became on-chart (LogMAR ≤1.6) at visit of interest.

- Eyes with change from baseline of at least -0.3 LogMAR at visit of interest
- Eyes with change from nadir of at least -0.3 LogMAR at visit of interest
- Eyes with change from baseline of at least -0.2 LogMAR at visit of interest
- Eyes with change from nadir of at least -0.2 LogMAR at visit of interest
- Eyes with BCVA < 1 LogMAR at visit of interest
- Eyes with BCVA ≤ 1 LogMAR at visit of interest
- Switch from baseline off-chart to on-chart (LogMAR ≤1.6) at visit of interest
- Number/percentage of on-chart eyes at visit of interest

LogCS

The following responders analyses will be performed on all eyes, all GS010 eyes and all sham eyes.

- Eyes with an improvement of at least 0.3 LogCS compared to baseline.
- Eyes with an improvement of at least 0.3 LogCS compared to nadir LogCS.
- For eyes with on-chart LogCS at baseline, an improvement of at least 0.3 LogCS compared to baseline.

- Switch from baseline off-chart LogCS to on-chart at visit of interest

Subject Level – Subject Responder

At subject level, the best outcome observed in either eye will be considered.

LogMAR

Subject Responder analyses will be carried out at visit of interest for the following definitions:

- Subjects with CRR from baseline in at least one eye at visit of interest.
- Subjects with CRR from nadir in at least one eye at visit of interest.
- Subjects with an improvement of at least -0.3 logMAR compared to baseline in at least one eye at visit of interest.
- Subjects with an improvement of at least -0.3 LogMAR compared to nadir in at least one eye at visit of interest.
- Subjects with an improvement of at least -0.2 logMAR compared to baseline in at least one eye at visit of interest.
- Subjects with an improvement of at least -0.2 logMAR compared to nadir in at least one eye at visit of interest.
- Subject with LogMAR BCVA value ≤ +1.0 LogMAR in at least one eye at visit of interest.
- Subject with LogMAR BCVA value < +1.0 LogMAR in at least one eye at visit of interest.
- For patients with both eyes off-chart at baseline, switch from baseline to on-chart (LogMAR ≤1.6) in at least one eye at visit of interest
- Number/percentage of on-chart patients (at least one eye on-chart) at visit of interest
- Clinically Relevant stabilization (CRS): Patient having a LogMAR < 1.0 at baseline in at least one eye that was maintained in this eye at the time point of interest (final BCVA)
- Clinically Relevant Benefit (CRB): Treatment benefit manifests as a clinically relevant stabilization (CRS) or a clinically relevant recovery (CRR) from nadir or both

For the subject responder endpoint, a randomization test will be performed for each of the follow-up visits (Years 2, 2.5, 3, 4 and 5):

- Response status of subjects whose ETDRS scores of the treated eye are at least 15 letters better than the sham eye or whose treated eye has a LogMAR acuity of at least 0.3 LogMAR better than the sham eye at each long-term follow-up visit.

LogCS

Subject Responder analyses will be carried out at visit of interest for the following definitions:

- Subjects with an improvement of at least 0.3 LogCS compared to baseline in at least one eye.
- Subjects with an improvement of at least 0.3 LogCS compared to nadir LogCS in at least one eye.
- For subjects with both eyes off-chart LogCS at baseline, switch from baseline to on-chart LogCS in at least one eye at visit of interest

8.5.2.5 Humphrey Visual Field Parameters

Mean deviation (MD) in decibels of sensitivity and foveal threshold sensitivities will be summarized by all eyes, all-GS010 eyes and all-sham eyes; along with change from baseline to each follow-up visit, using summary statistics for continuous variables.

The changes from baseline to 5 years of each data point of HVF, with the following thresholds of gain or loss: ≥7 dB; 5-6.99 dB; 3-4.99 dB; ≤2.99 dB, will be provided. Data of each individual patient (2 HVFs results per patient) will be described.

8.5.2.6 Goldmann Applanation Tonometry

Intraocular pressure (IOP) measurement (mmHg) in each follow-up visit and change from baseline to follow-up visits (Years 2, 2.5, 3, 4, and 5) will be summarized by all-GS010 eyes and all-sham eyes using summary statistics for continuous variables. Ocular and Slit-Lamp Examination

The result (normal/abnormal) before pupil dilation and after dilation for baseline and all follow-up visits (Years 2, 2.5, 3, 4, and 5) will be summarized by all-GS010 eyes and all-sham eyes and anatomical location using counts and percentages.

Quality-of-Life Analyses

Total scores and change of VFQ-25 and SF-36 scores (all individual domains and subdomains) from baseline to each follow-up Visit (Years 2, 3, 4, and 5) for all subjects will be assessed and summarized descriptively. Note that results will be presented in all subjects only, as all subjects are treated with GS010.

8.5.3 Methods for Handling Dropouts and Missing Data

Methods for dealing with missing data are detailed in Section 5.5.

8.5.4 Multiplicity

The primary objective of this study is to assess the long-term safety of intravitreal GS010 administration up to 5 years post-treatment in subjects who were treated in the RESCUE or REVERSE studies. All efficacy analysis will be secondary analysis. No adjustment of multiplicity will be applied.

8.6 SAFETY ANALYSES

All safety analysis will be conducted on the Safety Population and summarized by treatment actually received.

8.6.1 Adverse Events

All adverse events analyses will be presented with number of patients with at least one AE and number of events.

Primary Safety Analysis

The primary safety variables are:

- Adverse events (AEs) or serious adverse events (SAEs) (ocular or systemic) related to IMP (=GS010=study drug) or administration procedure, as judged by the Investigator, reported during the long-term follow-up visits (2, 2.5, 3, 4, and 5 years) from the period of 96 weeks up to 5 years post-treatment and summarized descriptively by type, frequency (number, percentage), severity, causal relationship, and seriousness.

Adverse events and SAEs related to study drug or study procedure will be summarized in two different ways: (1) systemic AEs and SAEs related to study drug or procedure or both, and (2) ocular AEs and SAEs related to study drug or procedure or both. Systemic AE data will be summarized by all subjects. Ocular AE data will be summarized by sham eye only, GS010 eye only, and both eyes.

The following summaries will be produced for (1) SAEs unrelated to study drug or procedure or both, (2) systemic AEs/SAEs related to study drug or procedure or both, and (3) ocular AEs/SAEs related to study drug or procedure or both, using counts and percentage as follows:

- Overall summary of AEs/SAEs related to study drug or procedure or both
- AEs related to study drug or procedure or both, including the number of events reported
- AEs/SAEs related to study drug or procedure or both by maximum severity
- AEs/SAEs related to study drug or procedure or both leading to study discontinuation
- SAEs related to study drug or procedure or both
- SAEs related to study drug or procedure or both leading to death.

Note that AE summaries will be provided for AEs collected during the originating study (RESCUE or REVERSE studies), for the follow-up period of CLIN-06, and combined.

Events will be coded using the current version of MedDRA and summarized by system organ class (SOC) and preferred term (PT).

Secondary Safety Analysis

The secondary safety endpoints are:

- Ocular or vision-related adverse events reported during the post-treatment long-term follow-up visits from the period of 96 weeks up to 5 years and summarized descriptively by type, frequency (number, percentage), severity, causal relationship, and seriousness.

The number, type, frequency, and severity of ocular or vision-related AEs, including those with no relation or any relation to the study drug or procedure will be presented in the same way that the primary endpoint of ocular AEs/SAEs related to study drug or procedure.

Listings of AEs, SAEs, ocular AEs, and AEs leading to death will also be presented.

Events will be coded using the current version of MedDRA and summarized by system organ class (SOC) and preferred term (PT).

A summary of AEs leading to discontinuation will be provided, grouped by system organ class and preferred term. A further tabulation presenting the preferred terms for the events in descending order of frequency will also be presented. All AEs recorded on the eCRF will be listed.

8.6.2 Laboratory Data

Parameters analyzed by the central laboratory will be used for statistical analysis. The laboratory test includes the following:

- Hematology tests and other blood laboratory tests: Complete blood count including red blood cells, hemoglobin, hematocrit, white blood cells with differential counts and platelets.
- Blood chemistry tests: Glucose, lipase, amylase, calcium, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN) and creatinine.
- Liver function tests: AST, ALT, ALP, γGT, total bilirubin and albumin

The statistical analysis of clinical laboratory tests will be conducted as described below.

Descriptive analysis (number of subjects, mean, SD, median, Q1, Q3, minimum, maximum) of each parameter at each time point and the changes from baseline;

Individual data listings of laboratory results will be presented for each subject at all study visits (scheduled and non-scheduled), including normal range limits for each laboratory test.

Out-of-range results will be flagged, and determinations of whether the results were considered to be of clinical significance by the investigator will be included. Clinically significant abnormal lab values for different parameters will be summarized at each post baseline time point.

Additionally, a summary will be presented of subjects who had an out-of-range result, including the subject, visit date, baseline value, normal range and out-of-range value observed.

8.6.3 Vital Signs

Systolic and diastolic blood pressure, pulse rate and body temperature will be displayed in summary tables including number of subjects, mean, SD, median, Q1, Q3, minimum and maximum by Visit. The descriptive statistics for change from baseline will be presented in the same way.

Individual data listings of systolic and diastolic blood pressure, pulse rate and body temperature will be produced for all subjects over time.

8.6.4 Physical Examinations, ECGs, and Other Observations Related to Safety

8.6.4.1 Physical Examination

All physical examination data will be listed by subject. No summary tables or analysis will be produced.

8.6.4.2 Electrocardiogram

The number and percentage of subjects with normal, abnormal clinically significant and abnormal but not clinically significant ECG findings will be summarized by Visit.

All ECG data will be listed by subject.

8.7 EXPLORATORY ANALYSES

8.7.1 Exploratory efficacy analyses

As an exploratory analysis, the response to treatment through Visit 5 (Year 5) using a MMRM model will be performed. The change from baseline in the LogMAR will be the response. Change from baseline of all-GS010 eyes will be compared to the change from baseline of all-sham eyes. The model will include subject as a random factor and fixed effects for treatment, follow-up visit (time point), eye status at baseline (better or worse), time from onset of disease and LogMAR at baseline as a covariate. The following interactions will be explored: baseline LogMAR and treatment; time from onset of disease and treatment; and eye status at baseline and treatment. The estimate of treatment effect at various follow-up time points and its 95% confidence interval (CI) will be presented. A UN@AR(1) (Autoregressive(1)) covariance structure will be fit to accommodate the doubly repeated measures data (repeated over time and eye). In the event of convergence problems with this covariance structure, other covariance structures will be explored.

Time course analysis of log of contrast sensitivity (LogCS), Humphrey visual field parameters and SD-OCT parameters will be conducted similarly to the time course analysis of LogMAR.

Other exploratory analyses will be performed for all analysed visits as a sensitivity analysis, excluding off-chart evaluations whose distance to the subject was superior to 2 meters. The endpoints analysed will be the ones described in 8.5.2.2 at eye level.

Additional exploratory analyses may be performed in the study.

8.7.2 Exploratory safety analyses

In order to perform following analyses, a medical review will be done to review all ocular AEs and classify them as Intraocular inflammation AE / Elevation of IOP AE (including the following terms: IOP increase, intraocular hypertension).
Additional medical review will be performed to identify concomitant treatments categories:

- Local IOP lowering agent,
- Systemic IOP lowering agent,
- Combination local and systemic lowering agents
- Local (topical) Corticosteroid (CS),
- Systemic CS.
- Combination local (topical) and systemic CS

The following descriptions will be made for GS010 eyes, SHAM eyes and overall.

8.7.2.1 Treatment for AEs related to elevation of IOP

Treatment of AEs with elevation of IOP will be described with number of eyes and events using treatment (None/IOP agent lowering local alone/IOP agent lowering systemic alone/ local and systemic in association) during the long-term follow-up visits (2, 2.5, 3, 4, and 5 years).

Duration of treatment will be described.

8.7.2.2 Treatment for AEs related to intraocular inflammation

Treatment of AEs related to an intraocular inflammation will be described with number of eyes and events using corticoids (None/local CS alone/systemic CS alone/ local and systemic in association) during the long-term follow-up visits (2, 2.5, 3, 4, and 5 years). Number and percent of inflamed eyes will be described for each type of CS (local CS alone/systemic CS alone/ local and systemic in association) during the long-term follow-up visits (2, 2.5, 3, 4, and 5 years).

Duration of treatment under CS will be described.

8.8 CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

The following changes from the analyses planned in the protocol were made in the SAP based on previous experience from RESCUE and REVERSE studies. These updates are not in contradiction with the protocol; as some analyses are considered not valuable or necessary for the current study, they are therefore removed from the plan.

- The additional statistical models for the LogMAR primary analysis for the EMA and FDA, that were planned to add the treatment by geographical interaction for lack of generalizability of treatment effect, will not be performed. The main-effect test will still be performed.

- As per the protocol, QoL assessments should have been collected at Visit 2 (Year 2.5). However, because it was decided it was not required, these data were therefore not collected and will not be summarized.
- Change of ganglion cell layer (GCL) thickness and topographical map will not be a part of the analyses as these data will not be assessed as initially planned in the protocol.
- The Pediatric Population and subset populations are included in addition to the populations included in the protocol. Selected outputs are also planned to be produced based on these populations.
- For doubly repeated measures MMRM models, the protocol specified that: "Compound symmetry structure will be fitted. In case of any convergence problem with this covariance structure, other covariance structures will be used." Following further statistical considerations, UN@AR(1) (Unstructured @ Autoregressive(1)) covariance structure will used instead. In case of any convergence problem with this covariance structure, other covariance structures will be explored.
- According to the protocol, the subject and the eyes of the subject were considered random effect in the statistical model. The analyses will not include the eyes of the subjects as a random effect.
- GEE models will be used instead of McNemar tests. Logistic regression will be used in place of Fisher's exact tests. The new models will provide the opportunity to control for baseline.
- Time-course analyses are designated exploratory, as the building of the model with multiple effects and interactions is an exploratory exercise.
- A Per Protocol analysis population has been added for efficacy analyses.
- Graphical representations and regressions of OCT parameters were added
- Exploratory safety analyses were added to describe treatments of eyes with intraocular inflammation and elevation of IOP.

9. VALIDATION

Table, listing, and figure validation will be performed by independent programming and documentation of validation will be provided.

10. REFERENCES

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APPENDIX 1 GLOSSARY OF ABBREVIATIONS

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
ATC	Anatomic Therapeutic Classification
BCVA	Best-corrected visual acuity
CF	Count fingers
CI	Confidence Interval
CS	Contrast Sensitivity
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
GCL	Ganglion Cell Layer
GEE	Generalized Estimating Equation
HM	Hand Motion
HVF	Humphrey Visual Field
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IVT	Intravitreal
LHON	Leber Hereditary Optical Neuropathy
LOCF	Last Observation Carried Forward
LogMAR	Logarithm of the Minimal Angle of Resolution
LP	Light Perception
MD	Mean Deviation
mITT	Modified Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mtDNA	Mitochondrial DNA

Glossary of Abbreviations:	
MMRM	Mixed-effects Model with Repeated Measures
ND4	NADH dehydrogenase 4
NLP	No Light perception
ODS	Output Delivery System
PT	Preferred Term
PP	Per Protocol
Q1	First Quartile
Q3	Third Quartile
QoL	Quality of Life
RGC	Retinal Ganglion Cells
SAP	Statistical Analysis Plan
SAE(s)	Serious Adverse Event(s)
SD	Standard Deviation
SD-OCT	Spectral-Domain Optical Coherence Tomography
SF-36-v2	36-Item Short Form Health Survey, Version 2
SOC	System Organ Class
TEAE(s)	Treatment-Emergent Adverse Event(s)
TFLs	Tables, Figures, and Listings
VFQ-25	Visual Functioning Questionnaire 25
WHODD	World Health Organization Drug Dictionary