CLINICAL RESEARCH PROTOCOL

Protocol Title: Long-term Follow-up of *ND4* LHON Subjects Treated With GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials

Investigational Drug: GS010 (rAAV2/2-ND4)

Study Name: RESCUE and REVERSE Long-term Follow-up

Protocol Identifier: GS-LHON-CLIN-06 **IND Number:** 16538
Study Phase: III **EudraCT Number:** 2017-002153-11
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Protocol Amendment 1.0: Version 2.0, Date of Final: 17 September 2018

Sponsor:
GenSight Biologics
74 rue du Faubourg Saint-Antoine
75012 Paris
France

Contract Research Organization (CRO):
PRA Health Sciences
35 rue d'Alsace
92300 Levallois-Perret
France

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) Integrated Addendum to International Council for Harmonisation (ICH) E6 R1 as set forth in the ICH guidelines on GCP (ICH E6 R2 March 2018), European Union General Data Protection Regulation (2016/679), and applicable local regulatory requirements.

CONFIDENTIAL

1. SIGNATURES

Representatives of Sponsor and Contract Research Organization

I have read and agree to the Protocol Version 2.0 GS-LHON-CLIN-06, entitled 'Long-term Follow-up of *ND4* LHON Subjects Treated with GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials.' I am aware of my responsibilities under the guidelines of GCP ICH E6 R2, Integrated Addendum to ICH E6 R1, European Union General Data Protection Regulation (2016/679), local regulations (as applicable), and the study protocol. I agree to conduct the study according to these responsibilities.

Accepted for the Sponsor – GenSight Biologics:

Barrett Katz, MD, MBA	Chief Medical Officer
Print Name	Title
Signature	9.18.18
	Date

Accepted for the Contract Research Organization – PRA Health Sciences:

Marina Zimmerman	Senior Project Manager
Print Name	Title
	20 September 2018
Signature	Date

Coordinating Investigator Signature - Europe:

Patrick Yu-Wai-Man, MD, PhD	International Coordinating Investigator, Europe
Print Name	Title
	19 September 2018
Signature	Date

Coordinating Investigator Signature - United States :

Nancy Newman, MD	International Coordinating Investigator, United States
Print Name	Title
	18 September 2018
Signature	Date

Investigator

I have read and agree to the Protocol Version 2.0 GS-LHON-CLIN-06, entitled 'Long-term Follow-up of *ND4* LHON Subjects Treated with GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials.' I am aware of my responsibilities as an Investigator under the guidelines of GCP ICH E6 R2, Integrated Addendum to ICH E6 R1, European Union General Data Protection Regulation (2016/679), applicable regulations, and the study protocol. I agree to conduct the study according to these responsibilities and to appropriately direct and assist the staff under my control, who will be involved in the study.

Clinical Site: _____

Site Number: _____

Site Principal Investigator:

_____	_____
Print Name	Title
_____	_____
Signature	Date

2. STUDY SUMMARY

PROTOCOL NO.: GS-LHON-CLIN-06
TITLE OF STUDY: Long-term Follow-up of *ND4* LHON Subjects Treated With GS010 Ocular Gene Therapy in the RESCUE or REVERSE Phase III Clinical Trials
INVESTIGATIONAL CENTERS: The 7 investigational centers are located in the European Union (United Kingdom [1], France [1], Germany [1], and Italy [1]) and the United States (3) and will be the same centers as those used in the RESCUE and REVERSE studies.
STUDY PERIOD: The total study period for an individual subject will be 3 years. The study will be stopped when the last subject completes the last visit.
PLANNED STUDY DATES: The planned duration of the long-term follow-up is 5 years starting from approximately the end of 2017 and stopping towards the end of 2022.
OBJECTIVES: **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**: (1) 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. (2) To assess the quality of life (QOL) in subjects who were treated with GS010 in the RESCUE or REVERSE studies for up to 5 years post-treatment.
STUDY DESIGN: ***Background****:* Subjects with Leber Hereditary Optic Neuropathy (LHON) who participated in the RESCUE and REVERSE clinical trials were administered gene therapy with the investigational medicinal product (IMP), GS010, by a single intravitreal (IVT) injection in a single randomly-selected eye, while the fellow eye received a sham IVT injection. The European Medicines Agency Committee for Medicinal Products for Human Use guideline recommends a monitoring plan for the purpose of observing subjects for potential delayed adverse events (AEs) for up to 5 years post-treatment; hence, the main rationale for initiating this long-term follow-up study. ***Study Design****:* This will be a Phase III prospective non-interventional long-term follow-up clinical study of subjects previously treated with GS010 and sham during 2 Phase III studies—RESCUE and REVERSE. The long-term follow-up study will follow subjects over an additional 3 years, for a total of 5 years post-injection follow-up. The long-term follow-up study will include 5 visits at 2, 2.5, 3, 4, and 5 years after IMP injection. ***Assessments***: Safety, efficacy, and QOL variables will be assessed during each of the 5 long-term follow-up visits and descriptive summaries and statistical testing will be used for analysis of the data.
ENDPOINTS: **Primary Endpoint** 1) Adverse events (AEs) or serious adverse events (SAEs) (ocular or systemic) related to IMP 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. **Secondary Endpoints** 1) 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. 2) 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, from the RESCUE or REVERSE study baselines and pooled, to the follow-up study time points (2, 3, 4, and 5 years). 3) 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, from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time points (2, 2.5, 3, 4, and 5 years).

4) 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:
   a. 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. The McNemar test will be used for comparisons from the RESCUE or REVERSE study baselines and pooled, to each of the follow-up study time points (2, 2.5, 3, 4, and 5 years).
   b. Eyes that lose less than the 15 ETDRS letters (equivalent to an increase of less than 0.3 LogMAR) compared to the RESCUE or REVERSE study baselines and pooled.
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 (2, 2.5, 3, 4, and 5 years) in the RESCUE and REVERSE studies and pooled.
6) Time course of the response in eyes treated with GS010 IVT injection compared to eyes treated with sham IVT injection, for the BCVA reported with LogMAR, for parameters measured with HVF 30-2 and for parameters measured with SD-OCT, with comparisons from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years) using mixed-effects models with repeated measures (MMRM).
7) Time course of the response in eyes treated with GS010 IVT injection compared to eyes treated with sham IVT injection, for contrast sensitivity measured with the Pelli-Robson chart with comparisons from the RESCUE or REVERSE study baselines and pooled, to follow-up study time points (2, 3, 4, and 5 years) using MMRM.
8) Visual improvement as measured by LogMAR by analysis of covariance (ANCOVA) to determine the difference in improvement 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 from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years).
9) Change of ganglion cell layer thickness/volume and topographical map and other parameters measured by SD-OCT (e.g., retinal nerve fiber layer and quadrantal thickness analyses) 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, from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years) using MMRM.
10) Quality of life as measured with the Visual Functioning Questionnaire 25 (VFQ-25) and 36-Item Short Form Health Survey, version 2 (SF-36-v2) subject-rated instruments and summarized descriptively with within-group comparisons from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years).

STUDY POPULATION AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

The study population will include subjects who were treated with GS010 in either of the 2 Phase III trials—RESCUE and REVERSE. Subjects will have had vision loss and been diagnosed with LHON due to the G11778A point mutation in the mitochondrial *ND4* gene. Subjects will have received a single IVT injection of the gene therapy GS010 in a single randomly-selected eye in the RESCUE or REVERSE studies.

Subjects will provide informed consent and will be enrolled after all inclusion/exclusion criteria are met.

Inclusion Criteria:

1. Subject was treated with GS010 IVT injection in either of the RESCUE or REVERSE Phase III clinical studies.
2. Subject of legal consent age has provided informed consent; subjects that are not of legal consent age have undergone their country-approved clinical trial enrollment consent process.

Exclusion Criteria:

1. Subject is unwilling or unable to comply with the protocol requirements.
2. Subject has any medical or psychological condition that, in the opinion of the Investigator, may compromise his or her safe participation in the study.
3. Subject is taking or intending to take idebenone during the long-term follow-up study period.

NUMBER OF SUBJECTS: The study population is limited to the number of subjects treated in the RESCUE or REVERSE studies.
STUDY TREATMENT: Not applicable. No investigational medicinal product will be administered.
STUDY EVALUATIONS: **Safety Variables:** The safety variables in this study will be AEs and SAEs. **Efficacy Variables:** The efficacy variables in this study will be contrast sensitivity using Pelli-Robson; best-corrected visual acuity reported in LogMAR; parameters of HVF and SD-OCT; and general and vision-specific parameters affecting QOL. **Quality-of-Life Variables:** The general overall QOL variables are physical, social, and emotional functioning, bodily pain, mental health and general health perceptions, and vitality/energy, as judged by the subject. The vision-specific QOL variables are eyesight, eye discomfort, ability to read, seeing close objects, seeing distant objects, nighttime vision, seeing during movement/motion, peripheral vision, color vision, and effect of vision on work activities, as judged by the subject.

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3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Word or Phrase
AAV	adeno-associated virus(es)
AAV2/2	adenovirus-associated viral vector serotype 2
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BCVA	best-corrected visual acuity
CBER	Center for Biologics Evaluation and Research (FDA)
CF	count fingers
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human (EU)
CRF	case report form
CRA	clinical research associate
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
ETV	early termination visit
EU	European Union
FDA	Food and Drug Administration (United States)
GCL	ganglion cell layer
GCP	Good Clinical Practice
HVF	Humphrey™ visual field (test)
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat (population)
IVT	intravitreal
LHON	Leber Hereditary Optic Neuropathy
LogCS	logarithm of contrast sensitivity
LogMAR	Logarithm of the Minimal Angle of Resolution

Abbreviation	Word or Phrase
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects models with repeated measures
mtDNA	mitochondrial DNA
NIH	National Institutes of Health
OCT	optical coherence tomography
QOL	quality of life
rAAV2	recombinant adeno-associated virus 2
RNFL	retinal nerve fiber layer
SAE	serious adverse event
SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SF-36-v2	36-Item Short Form Health Survey, version 2
SLE	slit-lamp examination
SOP	standard operating procedure
SUN	Standardization of Uveitis Nomenclature
US/USA	United States/United States of America
VFQ-25	Visual Function Questionnaire 25
WHO	World Health Organization

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Function	Name and Contact Information
Sponsor:	GenSight Biologics 74 rue du Faubourg Saint-Antoine 75012 Paris France
Chief Medical Officer:	Barrett Katz, MD, MBA GenSight Biologics (Sponsor) 74 rue du Faubourg Saint-Antoine 75012 Paris France Email: bkatz@gensight-biologics.com Phone: +1 646-831-3799
Coordinating Investigator – Europe:	Patrick Yu-Wai-Man, MD, PhD Moorfields Eye Hospital, London University of Cambridge United Kingdom
Coordinating Investigator – United States:	Nancy Newman, MD Emory Eye Center Atlanta, Georgia USA
Contract Research Organization:	PRA Health Sciences 35 rue d'Alsace 92300 Levallois-Perret France
Pharmacovigilance Activities Vendor:	Voisin Consulting Life Sciences 3 rue des Longs Prés 92100 Boulogne-Billancourt France
Central Laboratory:	Eurofins Central Laboratory, B.V. Bergschot 71 4817 PA Breda The Netherlands Eurofins Central Laboratory, LLC 2430 New Holland Pike Building D, Suite 100 Lancaster, Pennsylvania 17601 USA

Function	Name and Contact Information
Central Ophthalmic Assessment Reader:	Annesley Eye Brain Center 1304 Society Drive Claymont, Delaware 19703 USA
Statistical Analysis of the Data:	Mohammed A. Khan, MPH, MSc Senior Biostatistician PRA Health Sciences 500 South Oak Way Green Park, Reading, Berkshire, RG2 6AD United Kingdom
International Clinical Project Manager:	Nelle Messeca GenSight Biologics 74 rue du Faubourg Saint-Antoine 75012 Paris France Email: nmesseca@gensight-biologics.com Phone: +33 1 85 73 76 68

5. INTRODUCTION

5.1 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.[3-5]

Three primary point mutations in the mtDNA are causative of LHON in approximately 90% of those affected. These point mutations, G3460A, G11778A and T14484C, occur respectively in the *ND1, ND4,* and *ND6* genes of the mtDNA, and all encode protein subunits of Complex I (CI) of the mitochondrial respiratory chain. The resultant dysfunction of CI and the respiratory chain lead to abnormal mitochondrial metabolic function, decreased adenosine triphosphate (ATP) production, and increased reactive oxygen species. This leads to cell death of the RGC and the resulting atrophy of the optic nerve.[3]

LHON manifests as acute to sub-acute, sequential, bilateral, painless vision loss. It is a bilateral disease, and the clinical manifestation is essentially predictive of bilateral involvement. Greater than 97% of patients are reported to have bilateral involvement at 12 months and occurrences of unilateral involvement in retrospective reports of cohorts with LHON are very rare.[6,7] A G11778A *ND4* cohort was studied in which 53% reported bilateral involvement in ≤ 2 months, and 80% reported bilateral involvement in ≤6 months.[8]

The clinical hallmark of LHON is central vision loss.[9] 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.[6,10] A prospective natural history study[8] 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.

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

Investigational Medicinal Product

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

or the Investigator's Brochure for a discussion of the IMP.

Generation of GS010 Safety Profile
For the profile of GS010 including the expected adverse events, please refer to the current version of the Investigator's Brochure. Investigators are also referred to Van Der Reis[11] and Jager[12] for review of IVT injection-associated adverse effects.

5.2.1 Benefit Assessment
The main potential benefit for subjects with LHON due to the G11778A *ND4* mutation who receive GS010 IVT is halting, reversal (neuroprotection) or improvement of vision loss due to disease progression (neuroenhancement). Statistical modeling of the vision test results from GS-LHON-CLIN-01 indicate that potential benefit from IVT injection of GS010 may be greater in subjects with relatively shorter vision loss duration and with relatively less vision loss at the time of GS010 IVT injection. The appropriately powered Phase III efficacy studies were required and pending analysis to confirm any potential benefit from IVT injection of GS010.

5.2.2 Risk Assessment
This study is not an interventional study and there are no risks from administration of any IMP or study procedure. The long-term follow-up study will assess the safety of gene therapy IMP GS010 that was administered in the RESCUE and REVERSE studies. The risks associated with gene therapy IMPs are as follows:

Risk of Immune Response: Although the eye is considered to be an immune-privileged site,[13] an expected risk is potential immune responses to the capsid and transgene. Immune reactions against the newly introduced foreign protein or a T-cell response to the capsid could lower the therapeutic efficacy or cause local inflammation. Immune reactions against adenovirus-associated viral vector serotype 2 (AAV2/2) will be monitored throughout the study. The AAV2/2 used in this study has been studied and employed in other ophthalmologic clinical trials such as type 2 trials and to date no major health concerns, including immunologic or clinical, have been reported.[14]

Insertional Mutagenesis: Adeno-associated viruses (AAV) are non-integrative viruses. Studies performed in vivo with mouse liver suggest that AAV vectors integrate into the host genome; however no direct evidence of tumorigenesis due to AAV2/2 integration or other AAV serotypes has been observed in all preclinical studies and clinical trial data accumulated so far. This risk is considered as minimal.

Germ-line Transmission: Based on preclinical and clinical data, the risk of germ-line transmission is low. The probability that a recombination event could occur is very low.

Dissemination: The risk of vector shedding after in vivo gene therapy depends on the route of administration and the vector dose administered. An exhaustive report gathered the bio-distribution and shedding data from pre-clinical and clinical studies obtained for the HADV-5 and AAV2/2 vector.[15] These studies conclude that the more compartments the viral vector has

to pass to reach a certain excretion route, the lower the risk of shedding is, due to either dilution of the viral vector, or degradation in case of passage through the stomach or interaction with the immune system. The possible consequence of leakage of the vector into the environment is expected to be low as shedding is minimal and transient. Nevertheless, recombination with endogenous pathogenic replication-competent adenovirus might occur, therefore leading to AAV2/2 replication.

5.2.3 Summary of Benefits: Risks

The overall risk-benefit balance of IVT injection of GS010 for the treatment of vision loss due to the *ND4* mutation causing LHON is not yet available as no formal clinical efficacy analysis has been provided at the time of planning of this long-term follow-up study. The IMP, GS010, is considered to be safe and well tolerated.

5.3 Study Rationale

The dramatic loss of vision in individuals with LHON is life-changing, disabling, and affects their families socially, emotionally, and financially. LHON greatly alters a patient's ability to perform daily activities, reduces a patient's autonomy, and particularly disrupts the ability to read. The quality of life (QOL) in patients with LHON remains poor, even relative to other forms of chronic vision loss of other etiologies.[16] LHON represents an urgent medical need.

Currently there is no approved therapeutic agent for the treatment of vision loss from LHON in the United States. The European Medicines Agency (EMA) provided conditional approval under exceptional circumstances for Raxone® (International Non-Proprietary Name [NN]: Idebenone) (Raxone® European Product Assessment Report 2015). A study of idebenone for the treatment of vision loss from LHON, caused by the three most common primary mutations (*ND1, ND4, ND6*), failed to reach its primary endpoint.[17] Vision loss from LHON remains an unmet medical need.

The IMP, GS010, is a replication-defective single-stranded DNA recombinant adeno-associated virus 2 (rAAV2) vector containing a codon-modified complimentary DNA (cDNA), encoding the human wild type mitochondrial NADH dehydrogenase 4 protein (rAAV2/2-ND4), under the control of the cytomegalovirus immediate early promoter in an intron-containing expression cassette (beta globin intron, HBB2), flanked by the viral inverted terminal repeats from AAV2/2. GS010 is under development for the treatment of vision loss in LHON when due to the G11778A *ND4* mitochondrial mutation.

GS010 has received orphan drug status in both the United States of America (USA) and the European Union (EU) (respectively #13 4120 and #EMA/OD/164/10). GenSight Biologics has completed the preclinical development stage and has conducted a Phase I/II safety and tolerability trial. Subsequently, 2 Phase III clinical studies, the RESCUE and REVERSE studies (NCT02652767 and NCT02652780, respectively) of GS010, were initiated in the USA and EU. Subjects in the RESCUE and REVERSE were treated with the gene therapy IMP GS010 injected once in a single, randomly selected eye. The fellow eye received a sham IVT injection per the randomized treatment allocation. This long-term follow-up study will be considered part of the Phase III program and is an extension of the post-treatment 2-year

follow-up period.

Long-term Risk Assessment and Management

According to the EMA Committee for Medicinal Products for Human Use Guideline, entitled "Follow-Up of Patients Administered with Gene Therapy Medicinal Products," and the United States Food and Drug Administration (US FDA) Center for Biologics Evaluation and Research Guidance for Industry (2006) entitled, "Gene Therapy Clinical Trials: Observing Subjects for Delayed Adverse Events," viral vectors without integration, latency, or reactivation potential like AAV vectors present a low risk for gene therapy-related delayed adverse reactions. Although the FDA indicated that long-term follow-up is not considered necessary for this clinical development program, the EMA recommends a yearly monitoring plan up to 5 years post-treatment.

The regulatory intention of further observation is to determine the sustainability of efficacy, or whether declining efficacy after administration of gene therapy IMP occurs or whether more time is needed for tissue to be fully functional. For safety, the intention is to determine delayed-onset of adverse events (AEs), and to determine any additional unexplored long-term risks. The EMA refers to the Guideline (2008) entitled "Safety and Efficacy Follow-up: Risk Management of Advanced Therapy Medicinal Products" for possible delayed risks. One area for long-term observation is the potential risk directly related to the administration procedure of advanced therapies, and for this program would be the technique of IVT injection and any associated long-term effects.

In summary, all treated subjects in the RESCUE and REVERSE studies will be offered participation in the GS-LHON-CLIN06 study for the purpose of long-term safety evaluations, but only those providing informed consent and meeting eligibility criteria will be included in the study.

6. STUDY OBJECTIVES

6.1 Primary Study Objective

The primary objective of the 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.

6.2 Secondary Study Objectives

The secondary objectives of the study are:

1. 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.

2. 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.

7. INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

This study will be 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.

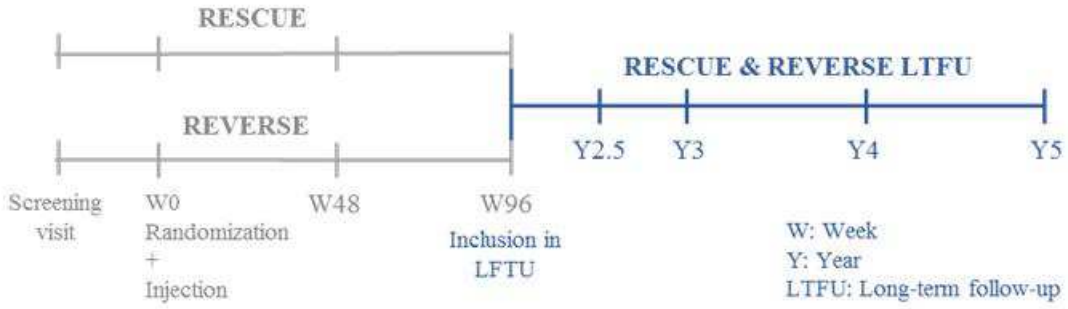
Subjects will be enrolled in the long-term follow-up study when informed consent is provided and inclusion/exclusion criteria are met. Enrollment will occur during the Inclusion Period, which will be during the RESCUE and REVERSE study Week 96/End-of-Study (EOS) Visit or anytime up to 1 day prior to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

The study population will be limited to the number of subjects treated in the RESCUE and REVERSE studies. The total length of the long-term follow-up study will be 3 years and the total length of the subject follow-up from IMP administration will be 5 years. The RESCUE and REVERSE long-term follow-up study is planned to start towards the end of 2017 and study start will be defined as the first subject's first visit in this study. The approximate study end date is planned to be towards the end of year 2022 after the last subject's last visit.

The follow-up will include onsite assessments of safety, QOL, and efficacy as in the RESCUE and REVERSE studies. The study will include 5 follow-up study visits: at 2.0-, 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.

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 W96 up to 1 day prior to Y2.5.

7.2 Study Endpoints

7.2.1 Primary Study Endpoint

The primary study endpoint is:

1. Adverse events (AEs) or serious adverse events (SAEs) (ocular or systemic) related to IMP 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.

7.2.2 Secondary Study Endpoints

The secondary study endpoints are:

1. 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 and summarized descriptively by type, frequency (number, percentage), severity, causal relationship, and seriousness.

2. 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, from the RESCUE or REVERSE study baselines and pooled, to the follow-up study time points (2, 3, 4, and 5 years).

3. 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, from the RESCUE or REVERSE study baselines and

pooled, to each follow-up study time points (2, 2.5, 3, 4, and 5 years).

4. 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:

    a. 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. The McNemar test will be used for comparisons from the RESCUE or REVERSE study baselines and pooled, to each of the follow-up study time points (2, 2.5, 3, 4, and 5 years).

    b. Eyes that lose less than the 15 ETDRS letters (equivalent to an increase of less than 0.3 LogMAR) compared to the RESCUE or REVERSE study baselines and pooled.

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 (2, 2.5, 3, 4, and 5 years) in the RESCUE and REVERSE studies and pooled.

6. Time course of the response in eyes treated with GS010 IVT injection compared to eyes treated with sham IVT injection, for the BCVA reported with LogMAR, for parameters measured with HVF 30-2 and for parameters measured with SD-OCT, with comparisons from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years) using mixed effects models with repeated measures (MMRM).

7. Time course of the response in eyes treated with GS010 IVT injection compared to eyes treated with sham IVT injection, for contrast sensitivity measured with the Pelli-Robson chart with comparisons from the RESCUE or REVERSE study baselines and pooled, to follow-up study time points (2, 3, 4, and 5 years) using MMRM.

8. Visual improvement as measured by LogMAR by analysis of covariance (ANCOVA) to determine the difference in improvement 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 from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years).

9. Change of ganglion cell layer (GCL) thickness/volume and topographical map and other parameters measured by SD-OCT (e.g., retinal nerve fiber layer and quadrantal thickness analyses) 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, from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years) using (MMRM).

10. QOL as measured with the Visual Functioning Questionnaire 25 (VFQ-25) and 36-Item Short Form Health Survey, version 2 (SF-36-v2) subject-rated instruments and summarized descriptively with within-group comparisons from the RESCUE or REVERSE study baselines and pooled, to each follow-up study time point (2, 2.5, 3, 4, and 5 years).

7.3 Study Population

The study population will include subjects who were treated with GS010 in either of the 2 Phase III trials—RESCUE and REVERSE. Subjects will have had vision loss and been diagnosed with LHON due to the G11778A point mutation in the mitochondrial *ND4* gene. Subjects will have received a single IVT injection of the gene therapy GS010 in a single randomly-selected eye in the RESCUE or REVERSE studies.

Subjects will provide informed consent and will be enrolled after all inclusion/exclusion criteria are met.

7.3.1 Inclusion Criteria

Subjects **MUST** satisfy all the following entry criteria before they will be allowed to participate in the study:

1. Subject was treated with GS010 IVT injection in either of the RESCUE or REVERSE Phase III clinical studies.
2. Subject of legal consent age has provided informed consent; subjects that are not of legal consent age have undergone their country-approved clinical trial enrollment consent process.

7.3.2 Exclusion Criteria

If any of the following apply, the subject **MUST NOT** enter the study:

1. Subject is unwilling or unable to comply with the protocol requirements.
2. Subject has any medical or psychological condition that, in the opinion of the Investigator, may compromise their safe participation in the study.
3. Subject is taking or intending to take idebenone during the long-term follow-up study period.

7.3.3 Subject Withdrawal/Early Subject Termination

In accordance with the Declaration of Helsinki and the applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects will be withdrawn from the study under any of the following circumstances:

- The subject's request, at any time and for any reason.
- The Investigator decides that the subject should be withdrawn and the study is not in the subject's best interest. The Sponsor or Sponsor designee is to be notified immediately.

- The Investigator, the Sponsor, or the Health Authority, for any reason, stops the study.
- The subject fails to return to the investigational site for scheduled visits and does not respond to telephone or written attempts at contact.

    - If the subject fails to attend the scheduled visit, there will be at least 2 attempts to contact the subject via telephone and 2 written communications. If these receive no reply the subject will be considered lost to follow-up.

Subjects who are lost to follow-up, who dropped out, or who were discontinued will not be replaced.

The reason for withdrawal will be recorded in the clinical records and the electronic case report form (eCRF). All subjects who are withdrawn from the study will undergo an Early Termination visit (ETV).

Evaluations at Withdrawal

For any subject who is withdrawn before completing all study visits, the Investigator should:

- Perform an ETV
- Complete all appropriate eCRF pages, providing the date of and explanation for the subject's withdrawal/discontinuation.

7.4 Concomitant or Prohibited Therapy

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.

No intervention specific for LHON, the disease under study, will be allowed during this long-term follow-up study and subjects will not be permitted to enroll in any investigational trials.

Subjects may receive concomitant medications that are for indications other than the treatment of vision loss due to LHON, and these are allowed per the decision and discretion of the Investigator.

Idebenone (Raxone®; approved in Europe for LHON, but not in the US) will be prohibited during the study. If the subject starts idebenone during the long-term follow-up, this will be considered non-adherence to the protocol but will not disqualify the subject from continuing in the study.

Any other treatments that are considered necessary for the subject's welfare may be given at the discretion of the Investigator. Administration of concomitant medications must be reported in the appropriate section of the eCRF along with dosage information, dates of administration, and reasons for use. Generic names for concomitant medication should be used, if possible. The total daily dose should be filled in whenever possible.

7.5 Safety, Efficacy, and Quality-of-Life Variables

7.5.1 Safety Variables

The safety variables in this study will be AEs and SAEs.

7.5.2 Efficacy Variables

The efficacy variables in this study will be contrast sensitivity; BCVA reported in LogMAR; parameters of HVF and SD-OCT; and general and vision-specific parameters affecting QOL (see Section 7.5.3).

7.5.3 Quality-of-Life Variables

The general overall QOL variables are physical, social, and emotional functioning, bodily pain, mental health and general health perceptions, and vitality/energy, as judged by the subject.

The vision-specific QOL variables are eyesight, eye discomfort, ability to read, seeing close objects, seeing distant objects, nighttime vision, seeing during movement/motion, peripheral vision, color vision, and effect of vision on work activities, as judged by the subject.

8. STUDY ASSESSMENTS AND PROCEDURES BY VISIT

8.1 Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with International Council for Harmonisation (ICH) GCP and all applicable regulatory requirement(s). Since this study will be collecting long-term follow-up assessments, the informed consent must include the expected duration of the subject's participation and the time intervals between site visits.

Logistically, the informed consent will be obtained prior to performing any study related procedures or documenting any subject data in the eCRF. If the subject does not want to commit to enrolling in the long-term follow-up study during the last visit (W96) of the RESCUE/REVERSE study, then subject may have up to 1 day prior to Visit 2 to sign the informed consent form (ICF). It will be explained and agreed to by the subject as part of the informed consent that assessment data from the RESCUE/REVERSE clinical database may be used as needed in order to complete the required data summaries and statistical analyses for the long-term follow-up study.

It will be recommended that the subject inform their primary physician about their participation in the RESCUE/REVERSE long-term follow-up study.

8.2 Schedule of Events

The Schedule of Events (**Table 1**) provides the procedures/assessments to be performed at each scheduled visit for long-term follow-up period.

The inclusion assessments may be performed at the Week 96/EOS visit of RESCUE/REVERSE and up to 1 day prior to the Visit 2 (Year 2.5 visit [up to 180 days post Week 96]).

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.

8.3 Visit 1: Inclusion Period (Year 2)

The Inclusion Period will start on the date of the last visit (W96) of the RESCUE/REVERSE study and end 1 day prior to Visit 2 (Year 2.5, Day 179) of the long-term follow-up study.

Ideally, the Visit 1 should be combined with the Week 96/EOS visit of RESCUE/REVERSE. If this is not possible, a separate Visit 1 will be scheduled during the Inclusion Period to sign the informed consent, review eligibility criteria, review AEs/SAEs and concomitant medications, and perform any additional assessments that were not completed during the Week 96/EOS visit of RESCUE/REVERSE.

The following assessments will be performed during the Inclusion Period in the approximate order listed:

- Review and update medical, surgical, and prior medication history
- Physical examination and vital signs
- Review of inclusion/exclusion criteria
- Review concomitant medication
- AEs/SAEs
- Clinical laboratory testing (hematology and serum chemistry including liver function)
- ECG
- VFQ-25 questionnaire
- SF-36v2 questionnaire
- Ocular and vision assessments
    - Refraction for BCVA, performed prior to pupil dilation
    - Visual acuity assessment, performed prior to pupil dilation
    - HVF 30-2, performed prior to pupil dilation
    - Goldmann applanation tonometry for intraocular pressure (IOP) measurement, performed prior to pupil dilation
    - Pelli-Robson contrast sensitivity, performed prior to pupil dilation
    - Slit-lamp examination (SLE) performed pre- and post-pupil dilation
    - SD-OCT, performed after pupil dilation

- Color fundus photography after pupil dilation.

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

The following assessments/procedures will be performed:

- Review concomitant medication
- Adverse events/SAEs
- Ocular and vision assessments
  - Refraction for BCVA, performed prior to pupil dilation
  - Visual acuity assessment, performed prior to pupil dilation
  - HVF 30-2, performed prior to pupil dilation
  - Goldmann applanation tonometry for IOP measurement, performed prior to pupil dilation
  - SLE performed pre- and post-pupil dilation
  - SD-OCT, performed after pupil dilation
  - Color fundus photography after pupil dilation.

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

- Review concomitant medication
- Adverse events/SAEs
- VFQ-25 questionnaire
- SF-36v2 questionnaire
- Ocular and vision assessments
  - Refraction for BCVA, performed prior to pupil dilation
  - Visual acuity assessment, performed prior to pupil dilation
  - HVF 30-2, performed prior to pupil dilation
  - Goldmann applanation tonometry for IOP measurement, performed prior to pupil dilation

- Pelli-Robson contrast sensitivity, performed prior to pupil dilation
- SLE performed pre- and post-pupil dilation
- SD-OCT, performed after pupil dilation
- Color fundus photography after pupil dilation.

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

- Review concomitant medication
- AEs/SAEs
- VFQ-25 questionnaire
- SF-36v2 questionnaire
- Ocular and vision assessments
  - Refraction for BCVA, performed prior to pupil dilation
  - Visual acuity assessment, performed prior to pupil dilation
  - HVF 30-2, performed prior to pupil dilation
  - Goldmann applanation tonometry for IOP measurement, performed prior to pupil dilation
  - Pelli-Robson contrast sensitivity, performed prior to pupil dilation
  - SLE performed pre- and post-pupil dilation
  - SD-OCT, performed after pupil dilation
  - Color fundus photography after pupil dilation.

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

- Review concomitant medication
- Adverse events/SAEs
- Physical examination and vital signs
- Clinical laboratory testing (hematology and serum chemistry including liver function)
- ECG

- VFQ-25 questionnaire
- SF-36v2 questionnaire
- Ocular and vision assessments
    - Refraction for BCVA, performed prior to pupil dilation
    - Visual acuity assessment, performed prior to pupil dilation
    - HVF 30-2, performed prior to pupil dilation
    - Goldmann applanation tonometry for IOP measurement, performed prior to pupil dilation
    - Pelli-Robson contrast sensitivity, performed prior to pupil dilation
    - SLE performed pre- and post-pupil dilation
    - SD-OCT, performed after pupil dilation
    - Color fundus photography after pupil dilation.

An early termination visit will include the EOS assessments.

8.8 Unscheduled Visit

Unscheduled visits may be performed anytime during the study 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.

If unscheduled visits occur, the Investigator must record the following in the subject's source document and eCRF:

- Reason for unscheduled visit
- AEs or SAEs as per Section 11.1.2.
- Recording of any changes or additions to concomitant medications (dose or regimen)
- Any clinical assessments, vision- and non-vision-related, deemed appropriate for the clinical care of the subject.

Unscheduled visits should not alter the timing of the routine study schedule.

9. DESCRIPTION AND METHODS OF STUDY ASSESSMENTS AND PROCEDURES

9.1 Demographics, Medical History, and Prior Medications

The baseline demographic data of age and gender will be imported from the RESCUE or REVERSE clinical database into the long-term follow-up clinical database.

The medical history will be reviewed and updated by the Investigator or qualified designee.

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 may be recorded as prior medications with respect to the long-term follow-up study.

9.1.1 Physical Examination

Physical examination will be performed by the Investigator, or designee, and will include general appearance, skin, head, eyes, ears, nose, throat, neck, thyroid, chest/lungs, heart, abdomen, lymph nodes, extremities; and subject height and body weight.

All abnormalities should be clearly documented. A clinically significant abnormal finding that is causally related to the study medication or study procedure in the judgment of the Investigator will be recorded as an AE.

9.2 Vital Signs

Vital signs will be assessed and recorded at Visit 1 and Visit 5/EOS or ETV by the Investigator or designee and will include temperature, pulse rate, and systolic and diastolic blood pressure (after sitting at rest for 5 minutes). A clinically significant abnormal finding that is causally related to the study medication or study procedure in the judgment of the Investigator will be recorded as an AE.

9.3 Electrocardiogram

A 12-lead ECG will be recorded at Visit 1 and Visit 5/EOS or ETV by the Investigator as part of the general safety assessment and will include R-R interval, PR interval, QRS complex, and QT interval. The ECG should be recorded prior to blood collection and the subject will be in a supine position and at rest for at least 10 minutes prior to the start of the recording. The ECGs will be reviewed and read locally at the investigative center site to assess any abnormalities of which should be clearly documented. A clinically significant abnormal finding that is causally related to the study medication or study procedure in the judgment of the Investigator will be recorded as an AE.

9.4 Clinical Laboratory Testing

Venous blood samples will be taken for hematology and chemistry testing at Visit 1 and Visit 5 (EOS) or ETV. The following parameters will be determined:

- Hematology: complete blood count including red blood cells, hemoglobin, hematocrit, white blood cells with differential counts, and platelets.

- Serum chemistry: glucose, lipase, amylase, calcium, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), and creatinine.

- Liver Function Tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γGT), total bilirubin, and albumin.

Analysis of samples will be conducted by the study central laboratory. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a Laboratory Manual.

Additional and repeat laboratory safety testing may be performed at the discretion of the Investigator.

The Investigator, or designee, is responsible to review the results of all laboratory tests in a timely manner. For all abnormal values, the Investigator must provide comments on the laboratory results sheet, identifying those that are abnormal and clinically significant, as well as those that are abnormal and not clinically significant. A clinically significant abnormal finding that is causally related to the IMP will be reported as an AE as per the Investigator's judgment.

9.5 Quality-of-Life Assessments

QOL questionnaires will be administered in paper version at the study site. An interviewer will administer the questionnaire to the subject. The caregiver may be present but this is not required. QOL questionnaires must be performed prior to any vision or ocular testing.

9.5.1 36-Item Short Form Health Survey, Version 2

The SF-36 Questionnaire is a generic subject-reported outcome instrument used to assess QOL. It includes 36 questions that assess 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)
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 (Ware 2007).

9.5.2 Visual Functioning Questionnaire-25

The VFQ-25 Questionnaire is a 25-item version of the 51-item Visual Function Questionnaire from the National Eye Institute. 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.[18]

9.6 Ocular and Vision Assessments

The methodology for all the ophthalmic evaluations will be detailed in the standard operating procedures (SOPs) for ocular and vision testing. A central ophthalmology reading center will be used for quality control and analysis as detailed per evaluation in the study specific SOP. Ocular and vision assessments will be performed by the Investigator or other qualified site personnel.

9.6.1 Pelli-Robson Contrast Sensitivity

Contrast sensitivity will be measured using the Pelli-Robson chart.[19,20] (Elliot 1990a, Elliott 1990b) The Pelli-Robson chart is comprised of eight rows of six optotypes of a constant size, with varying levels of contrast. The scoring will be based on the lowest contrast for which at least two letters in a triplet are reported correctly. The test will be administered at 1 meter. Assessment of the effect of GS010 will be analyzed.

9.6.2 Slit-Lamp Examination (Pre- and Post-Pupil Dilation)

Slit-lamp biomicroscopy examination will be performed per local standard medical examination techniques, pre- and post-pupil dilation, per the study schedule.

9.6.3 Goldmann Applanation Tonometry

Intraocular pressure will be measured per the study schedule by Goldmann applanation tonometry. Topical fluorescein and anesthetic will be utilized per standard local practices for the Goldmann applanation procedure.

9.6.4 Refraction for Best-Corrected Visual Acuity

Refraction will be performed as per the SOP for ocular and vision testing. Subject must be refracted prior to performing other vision assessments, for example visual acuity, contrast vision, and HVF testing. Refraction will be performed to obtain the BCVA for each eye.

9.6.5 Visual Acuity

Subjects will include both those with eyes able to read letters on the ETDRS chart, defined as on-chart eyes, and those with eyes unable to read letters on the ETDRS chart, defined as off-chart eyes. Please refer to the SOP for ocular and vision testing for the detailed definition of off- and on-chart eyes.

On-chart eyes will have an ETDRS score, as well as Snellen and LogMAR visual acuity values based on the letters/lines read on the ETDRS chart at 4- and 1-meter distances.

Off-chart eyes will not have an ETDRS score, Snellen or LogMAR visual acuity. Off-chart eyes will be tested for count fingers (CF) or hand motion (HM) visual acuity per the SOP for ocular and vision testing.

LogMAR visual acuity will be obtained for off-chart eyes based on the methodology described by Karanjia.[21] (Refer to the SOP for ocular and vision testing for complete details). Briefly, the finger/hand dimensions of the examiner will be measured beforehand. The examiner will then present their fingers/hand to the subject to assess CF or HM vision, and will measure the distance at which the subject accurately counted fingers or detected HM. The finger/hand dimensions of the examiner and the distance at which CF or HM was performed will be entered into the equation,[21] modified for assessment of visual acuity in meters. The output of interest is the LogMAR visual acuity.

For the purpose of the study, one ETDRS line will be considered equivalent to 0.1 LogMAR, and 1 ETDRS letter equivalent to 0.02 LogMAR.

9.6.6 Humphrey Visual Field 30-2

Standardized automated visual fields will be obtained with an HVF Analyzer II (Carl Zeiss Meditec Inc.) using the 30-2 SITA Fast test, Stimulus III White to measure mean deviations in decibels of sensitivity and other parameters obtained. A central reading center will perform quality control, analysis, and interpretation of all HVF results.

9.6.7 Spectral Domain Optical Coherence Tomography

SD-OCT will be assessed with the Spectralis® OCT (Heidelberg Engineering). Parameters will be obtained for the optic nerve (e.g., retinal nerve fiber layer [RNFL]) and posterior pole, per standard protocols included in the Spectralis software. A central reading center will perform quality control, analysis, and interpretation of all SD-OCT data.

9.6.8 Color Fundus Photos

Color fundus photos will be obtained at all visits and will be used for grading of vitreous haze. A central reading center will perform quality control, analysis, and interpretation of all color fundus photos.

10. SAFETY MEASUREMENTS AND VARIABLES

10.1 Adverse Events

10.1.1 Summary and Overview

An AE can be any unfavorable or unintended sign, including an abnormal laboratory finding, symptom or disease temporally associated with the IMP/study procedure, whether or not considered causally related with the IMP/study procedure.

Adverse events should be volunteered by the subject, be observed from examination of the subject at an investigative center visit, or from observations of clinically significant laboratory values or special examination abnormal values. AEs will not be solicited in this long-term follow-up study by the use of a specific list of anticipated events.

Surgical procedures planned before enrolment of the subject in the study are not considered AEs if the condition was known before study inclusion. In this case, the medical condition should be reported in the subject's medical history.

Worsening of visual acuity determined by the Investigator to be due to the progression of LHON will not be considered an AE.

10.1.2 Assessment and Documentation of Adverse Events

The Investigator will ask the subject at each follow-up visit how they have been doing since the last visit. The Investigator may inquire about any changes in their health status since the last visit and if the subject recalls and reports a health-related event to the Investigator, then the Investigator will use their medical judgment to determine whether the event is an AE. If the Investigator judges that the subject has had an adverse event, specific details will be explored for a complete AE assessment. If the subject is unable to recall specific details, the subject and/or Investigator may contact the subject's primary physician to collect the data needed for complete AE assessment. Further monitoring of AEs will occur for those AEs recorded on the eCRF.

AEs to be recorded on the eCRF and further monitored by the Investigator include the following:

- Any AE that is causally related to GS010 IVT and/or study procedure
- Any ocular or vision-related AE that is causally related or unrelated to study medication and/or study procedure
- Any SAE that is causally related or unrelated to study medication and/or study procedure.

Clinically significant abnormal findings observed during physical examination, vital signs measurement, or ECG recording will be recorded in the eCRF as an AE if the clinically significant abnormal finding is deemed as causally related to the study medication or study procedure.

Events are to be recorded by the Investigator or designee on the page titled "Adverse Events" of the eCRF (also called the "AE page"). The following AE data must be assessed and documented:

- Date of onset and date of resolution (i.e. actual dates when the event starts and is resolved rather than dates when the Investigator is informed).
- Nature/description of the event with self-explanatory and concise medical terminology (indicate a diagnosis or syndrome instead of symptoms). A diagnosis (a single diagnostic term), if available, should be used for documentation in the eCRF, rather than a subset of individual symptoms comprising the diagnosis; each diagnostic verbatim term will be counted as a single AE.
- Severity.
- Relationship to GS010 IVT injection.
- Relationship to study procedure.
- Seriousness.
- Any action taken regarding the event, whether by the Investigator, the subject (as reported by the subject), or by another physician (as reported by the subject or in the subject's medical record).
- Outcome.

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Any treatment given will be reported on the page "Concomitant medication" of the CRF.

If known, the name of any disorder or illness should be recorded, in preference to the listing of individual signs or symptoms.

Severity Intensity/Grading

The severity of clinical AE is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE scale will be provided to Investigators.

Should an event be missing in one of the scales, the following 3-point scale must be used:

- Mild: discomfort noticed, but no disruption of normal daily activity.
- Moderate: discomfort sufficient to affect normal daily activity.
- Severe: inability to work or perform normal daily activity.

Table 2 shows the correspondence between the severity levels of the CTCAE grades and the 3-point scale grades.

Table 2: Correspondence Between CTCAE and 3-Point Scale Severity Levels

CTCAE	3-Point Scale
1	Mild
2	Moderate
3/4/5	Severe

CTCAE, Common Terminology Criteria for Adverse Events

Relationship to IMP and/or Study Procedure(s)

The Investigator is requested to assess the relationship of any clinical adverse experiences to study treatment and/or study procedures. The relationship of each AE to the study treatment and/or study procedures will be evaluated using the following definitions:

- Unrelated: There is evidence of relationship to a cause other than the GS010 IVT injection or study procedure. Does not meet criteria listed under unlikely, possible, or probable.

- Unlikely: Does not follow a reasonable temporal sequence from administration of GS010 IVT injection or study procedure and is most likely produced by the subject's clinical state and/or by environmental factors and/or by other therapies administered.

- Possible: Follows a reasonable temporal sequence from administration of GS010 IVT injection or study procedure and is not likely produced by the subject's clinical state and/or by environmental factors and/or other therapies administered.

- Probable: Follows a reasonable temporal sequence from administration GS010 IVT injection or study procedure. Clear-cut temporal association.

- Related: Includes all of the following:
  - It follows a reasonable temporal sequence from administration of the drug.
  - It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject.
  - It follows a known pattern of response to the suspected drug.

Outcome

The outcome of each AE will be rated as follows:

- Recovered
- Not recovered
- Recovered with sequelae
- Fatal; This outcome is to be used only for an event leading to death. The outcome of all other events at the time of the death must be reported. The outcome of ongoing ones is reported as "not recovered".

- Unknown
- Worsening; This outcome is used when an AE worsens. The new status of the event is documented as another AE in the eCRF.

10.2 Serious Adverse Event Assessing and Recording

An SAE is any untoward medical occurrence or effect that fulfills the following criteria:

- Results in death;
- Is life-threatening;
- Requires hospitalization or prolongation of existing inpatient hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality/birth defect;
- Important medical events not captured by the above but which may, for example, require medical intervention to prevent one of the above criteria.

Definition of Serious Criteria

Life-threatening: an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).

Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery for a pre-existing condition that has not worsened, or hospitalization for routine clinical procedures that are not the result of an AE need not be considered AEs or SAEs. Any untoward event occurring during the procedure must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria. In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

Events Not to Be Considered an SAE

Events associated with hospitalization for the following will not be considered as an SAE:

- Evaluation or treatment of a pre-existing condition and a non-exacerbating condition as long as the condition(s) associated with the hospitalization:
  - Existed prior to the subject’s entry into the study and has been recorded in the subject’s medical history as documented in the CRF (e.g., degenerative disease)
  - Has not worsened in severity or frequency following the subject’s exposure to study medication
  - Has not required a change in treatment management following the subject’s exposure to the study medication.

- Treatment that is elective or has been planned in advance for a pre-existing condition and non-exacerbating condition.

Serious Adverse Event Documentation and Reporting
Reporting requirements for SAEs will be managed on behalf of GenSight by a third-party vendor.

Any SAE occurring during the course of the study, i.e., between the ICF signature and the EOS visit, **MUST be reported** to the Sponsor or their representative as soon as it becomes known. The Investigator must complete and email or fax a "Serious Adverse Event Form" to the Sponsor or their designee within 24 hours of occurrence or knowledge of the event.

An Investigator's delegate may complete the SAE form; however, the Principal Investigator or delegate physician must sign it. The form can be sent to the Sponsor or their designee with the delegate's signature if the Principal Investigator/delegate physician's signature cannot be obtained within one working day. The Principal Investigator/delegate physician's signature must be obtained as soon as possible, as must his/her evaluation of the relationship to the IMP. The signed form must be emailed or faxed to the Sponsor or their designee immediately.

The SAE form must be completed in English.

The initial report should be promptly followed by detailed, written reports, which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

The Sponsor or designee will assess initial and follow-up SAE reports from the site for expectedness, which will be determined based on the most recent edition of the Investigator's Brochure. Reports of Suspected Unexpected Serious Adverse Reactions will be expedited to the regulatory authorities as required per local regulations as an Investigational New Drug (IND) Safety Report within the required time frame.

The Sponsor or designee will be responsible for informing the institutional review board(s) (IRB)/independent ethics committee(s) (IEC) of SAEs as required. Correspondence with the IRB/IEC relating to the reporting of SAEs will be retained in the study file. The Investigator will receive a copy of all correspondence with the IRB/IEC and maintain in the site files.

10.3 Ocular Inflammation Events

Specific assessment and documentation of ocular inflammation will be of interest, as ocular inflammation is commonly reported with use of intravitreal AAV-based gene therapy and was a noted adverse side effect in preclinical studies, the Phase I/II, and initial Phase III clinical studies of the IMP GS010. Specifically, standardized schemes for assessing anatomic location, severity, and clinical evolution will be employed. Specific scales will be used for anterior uveitis (anterior chamber) and intermediate uveitis (vitreous).

The Standardization of Uveitis Nomenclature (SUN) Working Group provided standardized methods for (1) anatomic classification of uveitis (**Table 3**); (2) grading scheme for anterior chamber cells (**Table 4**); (3) grading scheme for anterior chamber flare (**Table 5**); and (4) activity of uveitis terminology (for clinical evolution) [22] (**Table 6**).

The National Institutes of Health (NIH) Grading System for Vitreous Haze is provided in **Table 7.**

Investigators will grade cases of ocular inflammation according to these scales.

Grading of anterior vitreous cells will be performed based on the slit-lamp examination utilizing a 1 mm by 1 mm slit-lamp beam and the same grading scheme used for anterior chamber cells (**Table 4**).

Grading of vitreous haze will be performed in a standardized fashion by the central ophthalmology reading center, based on color fundus photos of the posterior pole. Baseline color fundus photos will be obtained at Visit 1 (long-term follow-up study) for all subjects and fundus photos will be obtained at each visit thereafter. The NIH grading system[23] will be used to grade the vitreous haze on the fundus photo. **Table 7** and photos will serve as the basis for vitreous haze grading.

Table 3: Anatomic Classification of Uveitis (SUN Working Group)

Type	Primary Site of Inflammation[a]	Clinical Forms of Uveal Inflammation include:
Anterior uveitis	Anterior chamber	• Iritis • Iridocyclitis • Anterior cyclitis
Intermediate uveitis	Vitreous	• Pars planitis • Posterior cyclitis • Hyalitis
Posterior uveitis	Retina or choroid	• Focal, multifocal, or diffuse choroiditis • Chorioretinitis • Retinochoroiditis • Retinitis • Neuroretinitis
Panuveitis	Anterior chamber, vitreous, and retina or choroid	• Diffuse; all intraocular structures

SUN, Standardization of Uveitis Nomenclature
[a]As determined clinically. Adapted from the International Uveitis Study group anatomic classification.

Table 4: Grading Scheme for Anterior Chamber Cells and Anterior Vitreous Cells (SUN Working Group)

Grade	Cells in Field[a]
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

SUN, Standardization of Uveitis Nomenclature
[a]Field size is a 1 mm by 1 mm slit beam.

Table 5: Grading Scheme for Anterior Chamber Flare (SUN Working Group)

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

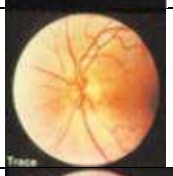
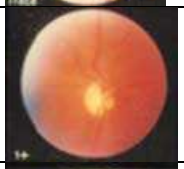
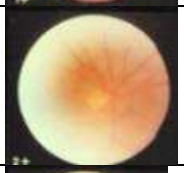
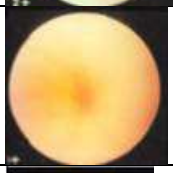
SUN, Standardization of Uveitis Nomenclature

Table 6: Activity of Uveitis Terminology (SUN Working Group)

Term	Definition
Inactive	Grade 0 cells[a]
Worsening Activity	Two step increase in level of inflammation (eg, anterior chamber cells, vitreous haze) or increase from Grade 3+ to Grade 4+
Improved Activity	Two step decrease in level of inflammation (eg, anterior chamber cells, vitreous haze) or decrease to Grade 0
Remission	Inactive disease for ≥ 3 months after discontinuing treatments for eye disease

SUN, Standardization of Uveitis Nomenclature
[a]Applies to anterior chamber inflammation.

Table 7: Vitreous Haze (National Institutes of Health)

Grade	Amount of Vitreous Flare/Haze	Illustration
0	No flare	
0.5+	Trace	
1+	Clear optic disc and vessels, hazy nerve fiber layer	
2+	Hazy optic disk and vessels	
3+	Optic disc visible	
4+	Optic disc not visible	
Quality Unsatisfactory	Photo quality inadequate for vitreous inflammation grading	
Not Performed	Photograph not performed	

Source: Nussenblatt RB et al. Ophthalmology. 1985;92:467-471.

10.4 Monitoring of Subjects with Adverse Events

Each subject must be carefully monitored for AEs. After an initial SAE report the Investigator is required to follow-up proactively each subject and provide further information to the Sponsor or designee on the subject's condition. Subjects who experience the onset of an AE thought to be related to IMP or IVT injection prior to their final visit (Visit 5/EOS) will be monitored until the resolution of the AE or for 30 days after the AE occurs, whichever comes first. AEs not resolved after 30 days will be listed in the CRF as continuing/not resolved.

10.5 Other Safety Assessments

10.5.1 Clinical Laboratory, Physical Examination, Vital Signs Parameters, and ECG

For laboratory parameters, physical examination findings, vital signs, and ECG any clinically significant abnormalities that are causally related to the study medication or study procedure in the judgment of the Investigator will be recorded as AEs.

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and monitored until the values have returned to the reference range and/or an adequate explanation of the abnormality is identified.

10.5.2 Concomitant Medications

During the study, any medication taken by the subject is to be reported by the subject. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy, and dose changes. The Investigator or designee will record any concomitant therapies given for the treatment of AEs on the concomitant medication page of the subject's source document and eCRF.

10.6 Procedures in Case of Pregnancy

If a subject or the partner of a male subject becomes pregnant during the study, the subject should inform the Investigator and provide a copy of the positive pregnancy test and estimated date of the pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) that begin before Visit 5 must be followed up and documented even if the subject was discontinued from the study. A pregnancy outcome of a congenital abnormality/birth defect or of a spontaneous miscarriage would qualify as an SAE and be reported to the Sponsor or designee for processing to the regulatory authorities. A pregnancy outcome of an elective abortion without evidence of complications would not be processed as an AE.

11. STATISTICAL ANALYSIS

Database lock, statistical programming and analysis, and reporting will be performed by the CRO.

11.1 Data Collection, Database Lock, and Coding of Terms

Electronic CRF/electronic data capture will be used for data collection during the long-term follow-up study and a Data Management Plan will be prepared by the CRO, PRA Health Sciences, detailing the procedures leading to database lock. Assessment data from the RESCUE/REVERSE clinical database that is needed to complete the statistical summaries and analyses that are required for this long-term follow-up study will be imported into the GS-LHON-CLIN-06 clinical database. When the GS-LHON-CLIN-06 clinical database has been found to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between GenSight Biologics and PRA.

Coexistent diseases and AEs will be coded using the current version of MedDRA. Previous and concomitant medications will be coded using the latest available World Health Organization (WHO) Drug Reference Dictionary.

11.2 Statistical Analysis Plan

A statistical analysis plan (SAP) will be prepared after the protocol is approved and before database lock occurs. The SAP will provide further details regarding the endpoints, data handling rules, and the statistical methods to be used to address all study objectives and endpoints. The SAP will also include display formats for the summary and analysis tables, listings, and graphical displays.

Data for quantitative variables will be presented by arithmetic mean (for other continuous variables), standard deviation (SD) median, first quartile (Q1), third quartile (Q3), minimum and maximum. Data for categorical and binary variables (responder analysis) will be presented by counts and percentages. Least square means, 95% confidence interval (CI) and P-values will be reported derived from models and statistical tests.

11.3 Sample Size Estimation

A formal sample size calculation will not be performed because this is an extension study and no inferential or formal statistics of the primary endpoint of the study will be conducted. The study population is limited to the number of subjects treated in the RESCUE and REVERSE studies.

11.4 Analysis Populations

11.4.1 Safety Population

The safety population will be defined as all 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.

11.4.2 Intent-to-treat Population

The intent-to-treat population will be defined as all 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 efficacy and QOL analyses. This

population is identical to the safety population.

11.5 Statistical Methods

11.5.1 Safety Analyses

Primary Safety Analysis

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

Clinically significant abnormal findings observed during physical examination, vital signs measurement, ECG recording, or laboratory values will be summarized as AEs in the AE tables if the clinically significant abnormal finding is deemed as causally related to the study medication or study procedure.

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

- Overall summary of AEs/SAEs related to study drug/procedure
- AEs related to GS010 IVT injection or study procedure, including the number of events reported
- AEs/SAEs related to GS010 IVT injection or study procedure by maximum severity
- AEs/SAEs related to GS010 IVT injection or study procedure leading to study discontinuation
- SAEs related to GS010 IVT injection or study procedure
- SAEs related to GS010 IVT injection or study procedure leading to death.

Events will be coded using the MedDRA and summarized by system organ class and preferred term.

Secondary Safety Analysis

The number, type, frequency, and severity of ocular or vision-related AEs, including those with no relation or any relation to the GS010 IVT injection or study procedure will be presented in the same way that the primary endpoint of ocular AEs/SAEs related to GS010 IVT injection or study procedure.

11.5.2 Secondary Long-term Efficacy Analysis

11.5.2.1 Pelli-Robson Contrast Sensitivity

Mean and standard deviation will be summarized at each follow-up visit, along with change from baseline to each follow-up visit, comparing all-GS010 eyes to all-sham eyes and best-GS010 eyes

to best-sham eyes; and worst-GS010 eyes to worst-sham eyes, using summary statistics for continuous variables.

11.5.2.2 LogMAR

Analysis for European Medicines Agency

The primary analysis will be performed on the intent-to-treat (ITT) 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 (intra-subject comparison) using a mixed-effects ANCOVA model using the following terms (or covariate) in the model:

- Subject and eyes of the subject as random factors
- The baseline LogMAR
- Treatment

The investigative site will not be included in this analysis as the number of subjects recruited per site will be very small. However, stratification by geographical area will 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 based on alpha of 0.05 (two-sided test).

An additional model will add the treatment by geographical interaction to investigate lack of generalizability of the treatment effect.

Analysis for Food and Drug Administration

The primary analysis will be performed on the ITT 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 center will not be included in the analysis as the number of subjects recruited per site will be very small. However, stratification by geographical area will be performed as a sensitivity analysis. Neighboring countries can be pooled together to reach at least 9 subjects per geographical entity. The pooling of countries will be performed during the masked review of data.

An additional model will add the treatment by geographical area interaction to test for a lack of generalizability of the treatment effect.

The same analysis will be repeated for worst-GS010 treated eyes against worst-sham eyes.

11.5.2.3 Parameters Measured with SD-OCT Including Ganglion Cell Layer Thickness/Volume and Topographical Map

The change of GCL thickness/volume and topographical map and other parameters measured by SD-OCT (e.g., retinal nerve fiber layer) from baseline to each follow-up visit will be based on mixed-effects ANCOVA, including the subject and the eyes of the subject as random factors, the treatment and the baseline GCL thickness/volume 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.

The analysis will also be performed for the best-GS010 treated eyes compared to best-sham eyes; and worst-GS010 treated eyes compared to worst-sham eyes. The analysis will be similar to the FDA analysis of change of LogMAR from baseline to the follow-up visits.

11.5.2.4 Responder Analysis

Eye responder and subject responder are defined in Section 8.2.2.

Responder analyses at all the follow-up visits will compare all-GS010 eyes against all-sham eyes based on a McNemar test. The analysis will also be performed to compare best-GS010 eyes against best-sham eyes and worst-GS010 eyes against worst-sham eyes using the Fisher exact test.

For the subject responder endpoint, randomization test will be performed for each of the follow-up visits.

11.5.2.5 Time Course Analysis

Time course analysis will compare time course of the response up to Visit 5 (Year 5) using MMRM (Mixed Model Repeated Measure) procedure. The change from baseline in the LogMAR and change from baseline in log of contrast sensitivity (LogCS) will be the responses. The change from baseline of all-GS010 eyes will be compared to the change from baseline of all-sham eyes using a MMRM including the subject and the eyes of the subject as random factors, the treatment, follow-up visit, eye status at baseline (better or worse), interaction between baseline values and treatment, interaction between linear time from onset of disease and treatment, interaction between eye status at baseline and treatment, interaction between linear time and treatment and baseline LogMAR as predictors in the model. The estimate of treatment effect at various follow-up time points and its 95% confidence interval (CI) (without adjustment for multiplicity) will be presented. Compound symmetry structure will be fitted. In case of any convergence problem with this covariance structure, other covariance structures will be used.

Time course analysis of Humphrey visual field parameters and SD-OCT parameters will be conducted similarly to the time course analysis of LogMAR (details will be provided in the SAP).

11.5.2.6 Humphrey Visual Field Parameters

Mean deviation in decibels of sensitivity and foveal threshold sensitivities at all the follow-up visits and change from baseline to each follow-up visit will be summarized by all-GS010 eyes against all-sham eyes; best-GS010 eyes against best-sham eyes; and worst-GS010 eyes against

worst-sham eyes, using summary statistics for continuous variables.

11.5.2.7 Goldmann Applanation Tonometry

Intraocular pressure measurement in mmHg in each follow-up visit and change from baseline will be summarized by all-GS010 eyes and all-sham eyes using summary statistics for continuous variables.

11.5.2.8 Ocular and Slit-Lamp Examination

The result (normal/abnormal) before pupil dilation and after dilation will be summarized by all-GS010 eyes and all-sham eyes and anatomical location using counts and percentages.

11.5.3 Quality-of-Life Analyses

Total scores from VFQ-25 and SF-36v2 and change from baseline to each follow-up visit will be summarized descriptively. All the individual domains and subdomains and change from baseline to each follow-up visit will also be summarized using descriptive statistics.

11.5.4 Concomitant Medication

Prior and Concomitant treatments will be coded using the WHO Drug Dictionary Version 01 Mar 2015 DDE, B2. For each medical entity, all Anatomical Therapeutic Chemical (ATC) codes will be assigned according 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 by WHO Drug Dictionary ATC levels (ATC1, ATC2) and preferred term.

11.5.5 Demographic and Baseline Characteristics Analysis

Demographic and baseline characteristics (age, gender, weight, height) will be summarized using descriptive statistics. Qualitative variables (gender) will be summarized using frequencies while quantitative variables (age, weight) will be summarized using mean, SD, median, Q1, Q3, minimum, and maximum.

11.5.6 Handling of Missing Data

In case of missing data, the imputation methods are described as follows:

Safety

Missing/partial start date and missing/partial end date for all TEAEs will be imputed. The rules will be detailed in the SAP.

11.5.7 Interim Analyses

Two interim statistical analyses are planned at completion of Visit 3 (Year 3) and Visit 4 (Year 4), in addition to the final analysis at Year 5 in the Clinical Study Report.

11.5.8 Data Monitoring Committee

Not applicable. No Data Monitoring Committee will be assembled for evaluation of results in this long-term follow-up study.

12. DATA MONITORING PROCEDURES AND QUALITY ASSURANCE

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines.

12.1 Data Collection and Data Management

Study-specific data outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator. Data will be verified electronically using a series of online programmed edit checks created by the Clinical Data Manager, and programmed by the Clinical Data Programmer or Designee. Data discrepancies will be brought to the attention of the clinical team and investigated by the clinical research associate (CRA) and site staff. The CRAs will review and verify all data collected in the eCRF against source documentation, during scheduled monitoring visits. The CRA will work closely with the site staff to address any discrepancies, so that proper resolutions can be made and documented in the clinical database. An audit trail will track all changes made to the data.

12.2 Database Quality Assurance

The clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification, using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the investigational site. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

12.3 Routine Monitoring

In order to maintain current of study progress, the Sponsor's monitors or representatives will visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. Onsite visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess subject enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study subjects considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. Adequate time and space for CRA monitoring visits should be made available by the Investigator.

The site must complete the CRFs in a timely manner and on an ongoing basis to allow review by the CRA.

12.4 Inspections and Auditing Procedures

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the investigative site during or after the study. The Investigator or designee should contact the Sponsor and CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are fulfilled.

13. STUDY MANAGEMENT AND MATERIALS

13.1 Electronic Case Report Forms

The Investigator is responsible for the quality of the data recorded in the eCRFs. The data entered should be a complete and accurate account of the subject's record collected during the study. Study data are not to be imputed directly into the eCRF, but must be collected first in primary source documents at the clinical site. Completion of source documents will precede the completion of the eCRF. Source documents may be electronic, hard copy, or a combination of both. Source documents are defined as the results of original observations and activities of a clinical investigation. They include, but are not limited to, progress notes, electronic data, screening logs, telephone interviews, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigators and made available for direct inspection by the authorized study personnel outlined in the ICF. The eCRF will be considered the source document for individual CRF elements such as study-specific scales if those data are collected directly onto a CRF.

Data collection will be completed according to the guidelines provided by the Sponsor or its designee in writing. All required data are to be recorded using the source documents for every subject who signed an informed consent. Site staff will be trained on the eCRF completion guidelines and requirements for source documentation.

Completed eCRFs will be reviewed by the study monitor in line with CRF review guidelines. The Sponsor or its designee will review every subject's eCRF and 100% source data verification (SDV) will be required for all data; and this includes the Annesley Brain Eye Center worksheets. Eligibility failure CRFs and source documents require 100% SDV. Any discrepancies found during the CRF review will be clarified by the Investigator or designated individual. This includes on-site CRF reviews by the Sponsor or its designee, or during quality assurance review of the data.

A justification must be documented for any missing data. Any changes in the study progress notes and other source documents will be initialed and dated by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (e.g., wrong data right data). If the reason for the change is not apparent, a brief explanation for the change will be written by the clinician in the source documentation.

The Investigator must sign and date a declaration attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study.

All eCRF entries, corrections, and alterations must be made by the Investigator or designated individual. The Investigator or designated individual must adjust the eCRF (if applicable) and complete the query.

13.2 Source Documents Maintenance

The Investigator must complete a subject identification and enrolment log to allow easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness. The subject identification and enrolment log should remain

confidential and will be filed in the Investigator Site File. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by assigned number only. The Investigator must also complete a subject eligibility log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

At a minimum, source documentation must be available to confirm: subject identification, eligibility, and study identification; explanation of the study and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs; concomitant medications; date of study completion or early discontinuation, and reason for early discontinuation if applicable.

The original signed informed consent for each subject shall be filed with records kept by the Investigator and a copy shall be given to the subject.

13.3 Record Maintenance

All documents pertaining to the study, including all versions of the approved study protocol, copy of the informed consent document, Health Insurance Portability and Accountability Act documents, completed eCRFs, source documents (e.g., subject records, hospital records, laboratory records, drug accountability records), and other study-related documents will be retained in the permanent archives of the study site.

The Investigator must therefore notify and obtain approval in writing from the Sponsor prior to destruction of any study records or provide an opportunity for the Sponsor to collect such records. If the Investigator withdraws from the study (e.g., relocation, retirement) all study-related records should be transferred, in a written agreement with the Sponsor, to a mutually agreed-upon designee within a Sponsor-specified timeframe.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, CRFs and study drug inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities.

If an Investigator moves, withdraws from an investigation or retires the responsibility for maintaining the records may be transferred to another person who will accept responsibility.

Notice of transfer must be made to and agreed by the Sponsor.

13.4 Confidentiality

All information obtained during the conduct of the study with respect to the subject's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each subject's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, subjects must not be identified by name. Instead, subjects will only be known by the unique subject number allocated to them in order to ensure confidentiality on all study documentation. Subjects will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure subject safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the competent authorities to review subjects' medical records as they relate to this study. Only the subject's unique number on the CRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

All subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol and the informed consent signed by the subject, unless otherwise agreed to in writing by the subject.

Documents that are not for submission to the Sponsor or the CRO will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying subjects by name will leave the investigative site and subject identity will remain confidential in all publications related to the study.

14. ADMINISTRATIVE REQUIREMENTS

14.1 Ethics Committee(s)

This study will be conducted in accordance with the Note for Guidance on GCP (ICH Harmonized Tripartite Guideline E6 [R2]; FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Fortaleza 2013) (available in the Investigator study file) and all applicable national and local regulatory requirements and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). Additionally, in Europe this study will be conducted in compliance with IEC, in accordance with applicable regulations regarding clinical safety data management (E2A, E2B[R3]), European Community directives 2001/20, 2001/83, 2003/94, 2005/28, and 2016/679 (General Data Protection Regulation) as enacted into local law. In the United States, this study will be conducted in compliance with IRB, Title 21 Part 56 of the USA Code of Federal Regulations (CFR) relating to IRBs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312) - in accordance with applicable ICH regulations regarding clinical safety data management (E2A, E2B[R3]).

14.2 Regulatory Approval

GenSight or their appointed agents will be responsible for ensuring that appropriate regulatory authority approvals are obtained, according to local country requirements. No subject may enter the study until this approval has been obtained. A copy of the approval (where one is provided, according to local country requirements) will be provided to the Investigator and to the IRB/IEC.

14.3 Protocol Compliance

In accordance with ICH Topic E6 (R2) Guideline for GCP the Investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and documented approval from the IRB/IEC of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]).

Protocol amendment(s) must be approved by the Sponsor and comply with national requirements. A protocol amendment must be submitted to the appropriate regulatory authorities and to the IRB/IEC assuming this responsibility. The Investigator must await IRB/IEC approval of protocol amendments before implementing the changes, except where necessary to eliminate apparent immediate hazard to subjects. In these cases, the IRB/IEC must be notified within 5 business days of the change. All amendments to the protocol must be approved by both the appropriate regulatory authorities and the IRB/IEC, except for administrative revisions, which require notification only.

14.4 Protocol Adherence and Deviations

Any protocol deviation related to the conduct of the study, subject management, or subject assessment will be documented and discussed with the Investigator on a case by case basis. Protocol deviations will not be approved prospectively.

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator. In the event of a significant protocol deviation due to an emergency, accident, or

error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

14.5 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and Investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory and other protocol-required services are being paid directly or indirectly.

The disclosure of any financial interests from each Investigator or sub-Investigator is required for this study, including financial interests of the spouse and each dependent child of the Investigator who is directly involved in the treatment or evaluation of research subjects that could affect the reliability of data submitted to regulatory authorities. Financial Disclosure Statements will need to be completed, as requested by FDA CFR 21 Part 54 for all US Investigators; and by EU Investigators if data from these sites will be used to support a New Drug Application in the US.

ICH requires that the clinical Investigator make all clinical trial-related records available for direct access by the CRA, auditor, IRB, or regulatory agency and that financial aspects of the trial be in the Investigator's files. The FDA currently does not require financial records or mandate "direct access" (312.62).

14.6 Insurance, Indemnity, and Compensation

GenSight undertakes to maintain an appropriate clinical study insurance policy. Deviations from the study protocol—especially the prescription of a dose other than that scheduled in the study protocol, other modes of administration, other indications, and longer treatment periods—are not permitted and shall not be covered by the statutory subject insurance scheme.

14.7 Investigational Site File Management

The Investigator is responsible for assuring that the Investigational Site Central File is maintained. The Site Central File will contain, but will not be limited to, the information listed as follows:

(1) Investigator’s Brochure;
(2) Current, signed version of the protocol;
(3) Protocol amendments (if applicable);
(4) Operations Manual (if applicable);
(5) Current ICF (blank);
(6) Curricula Vitae of Investigator(s) and sub-investigator(s) and photocopy of their respective license(s) where required by law; Original US FDA Form 1572 (for all studies conducted under US IND regulations), signed by all Principal Investigators. The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required the ICH GCP and by local or national regulations;
(7) Documentation of IRB/IEC approval of the protocol, the ICF, any protocol amendments, and any ICF revisions;
(8) All correspondence between the Investigator, IRB/IEC, and the Sponsor/CRO relating to study conduct;
(9) Lab certification(s);

(10) Monitoring log;
(11) Signature list of all staff entering data in the eCRF; and
(12) Signature list of all staff completing drug accountability summaries.

14.8 Discontinuation of the Study

This study may be terminated by the Sponsor. The study may also be terminated prematurely at any time when agreed to by both the Investigators and the Sponsor as being in the best interests of subjects, and justified on either medical or ethical grounds. In terminating the study, GenSight, the CRO (PRA) and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

14.9 Clinical Study Report

A final clinical study report will be prepared according to the ICH Guideline on Structure and Contents of Clinical Study Reports. A final clinical study report will be prepared regardless of whether the study is completed or prematurely terminated. The Sponsor will provide each Investigator with a copy of the final report for retention.

14.10 Publication Policy

After completion of the study, the Investigator(s) may prepare a joint publication with the Sponsor. The Investigator(s) must undertake not to submit any part of the data from this protocol for publication without the prior consent of GenSight.

15. REFERENCE LIST

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16. APPENDICES

Not applicable.