CLINICAL RESEARCH PROTOCOL

DRUG:	GS010 (rAAV2/2-*ND4*)
STUDY NUMBER(S):	GS-LHON-CLIN-03A
PROTOCOL TITLE:	A Randomized, Double-Masked, Sham-Controlled, Pivotal Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 (rAAV2/2-*ND4*) in Subjects Affected for 6 Months or Less by Leber Hereditary Optic Neuropathy Due to the G11778A Mutation in the Mitochondrial NADH Dehydrogenase 4 Gene
STUDY NAME:	RESCUE
PHASE:	III
SPONSOR:	**GenSight Biologics** 74 rue du Faubourg Saint-Antoine 75012 Paris France
[redacted]	[redacted]
EudraCT NUMBER:	2015-001265-11
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Clinical Trials.gov NUMBER:	NCT02652767
ORIGINAL PROTOCOL DATE:	08 May 2015
VERSION NUMBER:	4.0
VERSION DATE:	07 November 2016

CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: RESCUE Study: A Randomized, DoublE-Masked, Sham-Controlled, Pivotal Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 (rAAV2/2-*ND4*) in Subjects Affected for 6 Months or Less by Leber Hereditary Optic NeUropathy Due to the G11778A Mutation in the Mitochondrial NADH Dehydrogenase 4 GEne

Study No: GS-LHON-CLIN-03A

Original Protocol Date: 08 May 2015

Protocol Version No: 4.0

Protocol Version Date: 07 November 2016

This study protocol was subject to critical review and has been approved by the appropriate sponsor personnel. The information contained in this protocol is consistent with the current risk-benefit evaluation of the investigational product and the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of Good Clinical Practice and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

[redacted]

STUDY GS-LHON-CLIN-03A

RESCUE STUDY

A RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED, PIVOTAL CLINICAL TRIAL TO EVALUATE THE EFFICACY OF A SINGLE INTRAVITREAL INJECTION OF GS010 (rAAV2/2-*ND4*) IN SUBJECTS AFFECTED FOR 6 MONTHS OR LESS BY LEBER HEREDITARY OPTIC NEUROPATHY DUE TO THE G11778A MUTATION IN THE MITOCHONDRIAL NADH DEHYDROGENASE 4 GENE

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to GenSight Biologics is the confidential and proprietary information of GenSight Biologics, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of GenSight Biologics.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the guidelines for Good Clinical Practice and International Conference on Harmonization guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by GenSight Biologics or specified designees. I will discuss the material with them to ensure that they are fully informed about GS010 and the study.

_____

Investigator Name

_____

Investigator Signature

_____ _____

Date Site Number

STUDY SUMMARY

Title: RESCUE Study: A Randomized, Double-Masked, Sham-Controlled, Pivotal Clinical Trial to Evaluate the Efficacy of a Single Intravitreal Injection of GS010 (rAAV2/2-*ND4*) in Subjects Affected for 6 Months or Less by Leber Hereditary Optic Neuropathy Due to the G11778A Mutation in the Mitochondrial NADH Dehydrogenase 4 Gene

Rationale: Leber Hereditary Optical Neuropathy (LHON) is an inherited mitochondrial disease of partial penetrance affecting both genders with predominance in males (~80%). The pathophysiology of LHON mainly affects the retinal ganglion cells (RGCs). The *ND4* G11778A mutation is responsible for the majority of cases (~70%). Vision loss classically occurs in a bilateral sequential fashion, the second eye becoming involved after the first one with a median delay of 2 months. GenSight Biologics' strategy to specifically treat LHON is based on a gene therapy approach by the development of GS010. The scientific basis behind this Investigational Medicinal Product consists of rescuing mitochondrial function by reaching the nucleus of the target cell, forming intranuclear episomes that can be read and produce specific mRNA inducing ND4 protein synthesis and targeting of the ND4 protein to the mitochondria. This is expected to significantly improve the respiratory chain function. Preclinical studies performed in rats strongly suggest that GS010 displays a potential to restore wild-type ND4 expression.

Study Treatment: GS010 is a recombinant adeno-associated viral vector serotype 2 (rAAV2/2) containing the wild-type *ND4* gene (rAAV2/2-*ND4*). In this study, subjects will receive a single dose of GS010 *via* intravitreal (IVT) injection containing 9E10 vg in 90µL balanced salt solution (BSS) plus 0.001% Pluronic F68®.

Target Population: The study population will be subjects with LHON due to the G11778A *ND4* mutation who have been affected by vision decline for 180 days or less.

Number of Subjects: It is planned that approximately 40 subjects will be screened in order to randomize 36 into the study at 7 sites (one each in France, Germany, Italy, and the United Kingdom and 3 in the United States).

Objectives: **Primary Objective:**

To evaluate the efficacy of GS010 compared with sham at Week 48 in the change from baseline of the Log of the Minimal Angle of Resolution (LogMAR) in subjects affected for 6 months or less by LHON.

Secondary Objectives:

- To evaluate the efficacy of GS010 compared with sham over the follow-up period and at Week 96 in the change from baseline of the LogMAR.
- To verify whether the efficacy at Week 48 and at Week 96 of GS010 compared with sham and measured by the change from baseline in the LogMAR is dependent upon the treatment of the better- or worse-seeing-eye.
- To verify whether the rate of responders at Week 48 and 96 is dependent upon the treatment received and whether the magnitude of the treatment effect is dependent the treatment of the better- or worse-seeing eye at entry.
- To assess the effect of GS010 on parameters measured with high resolution spectral-domain optical coherence tomography (SD-OCT).
- To assess the effect of GS010 on standardized automated visual fields obtained with the Humphrey Visual Field (HVF) Analyzer II.
- To assess the effect of GS010 on contrast sensitivity measured with the Pelli-Robson chart.
- To assess the effect of GS010 on color vision measure with the Farnsworth-Munsell 100 Hue color test.

[redacted]

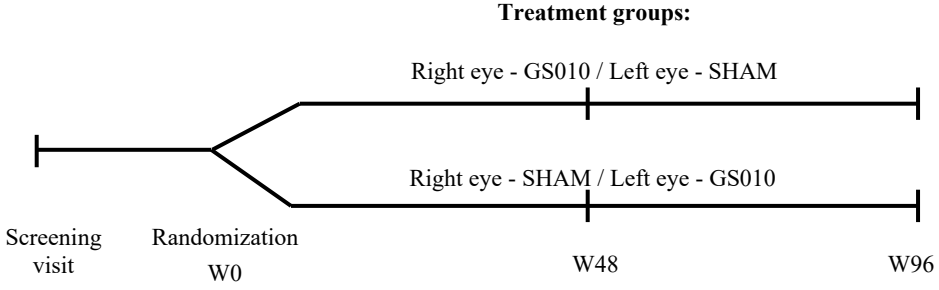
Study Design:

GS-LHON-CLIN-03A is a Phase III double-masked, sham-controlled, multicenter, multi-country study. Recruitment is competitive.

Both eyes will receive standard antiseptic preparation, administration of topical local ocular anesthetic agents and will undergo pupillary dilation. Administration of an intra-ocular pressure lowering agent will precede treatment. GS010 will be administered once during the study via a single IVT injection. Sham IVT injection will be performed by applying pressure to the eye at the location of a typical procedure using the blunt end of a syringe without a needle.

The right eye of each subject will be randomly allocated to receive either GS010 or sham treatment in a 1:1 allocation ratio. The fellow (left) eye will receive the treatment not allocated to the right eye. Therefore, each

subject will receive GS010 in one eye and sham treatment in the fellow eye.



An algorithm with a testing hierarchy will be employed to determine the better- and worse-seeing eye of each subject prior to randomization. The randomization will be based on the right and left eye, because if the right eye is treated the left eye will receive sham and vice versa the treatment groups will be automatically balanced. However, the better- or worse-seeing eye at entry can be a confounding factor, and it cannot be discarded that the treatment effect will be the same in the better and worse seeing-eye. Secondarily, in order to verify this hypothesis, an adaptive randomization technique called Efron's minimization method will be used to minimize the imbalance of treatment groups between the better-seeing eyes treated and worse-seeing eyes treated.

Masking will be accomplished with sham injection of the fellow eye. Thus treatment allocation will be double-masked for both the subject and the investigation (follow-up) team. The pharmacy team, as well as the physician and medical team performing the GS010 administration and sham injection will be unmasked to treatment allocation. This treating, unmasked medical team will also perform the first follow-up visit (Visit 4), as well as focused follow up of ocular adverse events (AEs) commencing at Visits 3 and 4 until resolution of the AE or the determination that no further clinical evolution is expected. Centralized analysis of the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity results, automated visual fields, SD-OCT, color vision and contrast sensitivity will be performed.

Trial visits:

The trial is divided into the following visits:

- Screening Visit (Visit 1): From 28 to 2 days before the investigational medicinal product (IMP) administration. This visit will allow Investigators to assess subject eligibility based on selection and non-selection criteria.
- Inclusion Visit (Visit 2): 1 day before the IMP administration.

This visit will allow Investigators to confirm the subject's eligibility based on inclusion and exclusion criteria. Subjects will undergo baseline ophthalmological testing.
After the subject is confirmed to be eligible for the study, the right eye will be randomized to GS010 or sham treatment based on a pre-defined central randomization scheme.

- Treatment Visit (Visit 3): Day of the IMP administration.
  Subjects will receive GS010 by IVT injection according to the randomized treatment assigned. The fellow eye will receive the alternative treatment.
- Follow-up visits (Visits 4 to 12): Nine follow-up visits after the IVT procedure will be conducted at 24 hours and 2, 4, 8, 12, 24, 48, 72, and 96 weeks.

The study plan is shown in Section 4.2.

A Data and Safety Monitoring Board meeting will be convened at least every 6 months to review the safety data.

Study duration:

Initiation of the trial with the first subject's first visit is planned for late Q4 2015. The estimated recruitment period is 12 months and will be dependent on recruitment rate. Total study follow-up is 96 weeks and the study will end with the last subject's last visit. The last subject's last visit is estimated to occur late Q4 2018. Therefore, the estimated study duration is 3 years.

At the end of this initial study period, a long-term safety and efficacy study as detailed in a future separate protocol will be initiated for further evaluation of the safety and efficacy durability. The long term safety study duration will be conducted according to current regulatory authority recommendation.

Primary Efficacy Endpoint:

The primary endpoint will be the ETDRS visual acuity (quantitative score) at Week 48 after IVT injection. The subjects' LogMAR scores, which are derived from the number of letters they read on the ETDRS chart, will be used for statistical analysis purposes. The change from baseline in each eye will be the primary response of interest.

Secondary Efficacy Endpoints:

- ETDRS visual acuity (quantitative score) over the follow-up period and at Week 96 after IVT injection. Change from baseline of the LogMAR scores will be used for statistical analysis purposes.
- Response status to treatment at Week 48 and 96 after IVT injection. Responder will be defined by an improvement of at least 15 letters in the visual acuity score obtained with ETDRS *or* being greater than a Snellen acuity equivalent of 20/200.
- Measure of parameters of high resolution SD-OCT of the posterior pole and optic nerve at Week 48 and Week 96.

- Measure of the standardized automated visual fields obtained with HVF Analyzer II. Mean Deviation (MD) in decibels of sensitivity will be used at Week 48 and Week 96.
- Measure of contrast sensitivity with the Pelli-Robson chart at Week 48 and Week 96.
- Measure of color vision with the Farnsworth-Munsell 100 Hue color vision test at Week 48 and Week 96.

[redacted]

Safety Endpoints:

- AEs and serious adverse events (SAEs), including those that are treatment-emergent and non-treatment-emergent, throughout the study period and at each study visit. Incidence and severity of systemic and local (ocular) AEs and SAEs will be determined at each clinical site and for the entire study cohort.

[redacted]

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LIST OF ABBREVIATIONS

AAV	adeno-associated viral vector, serotype 2
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCVA	best corrected visual acuity
BP	blood pressure
BSS	balanced salt solution
cDNA	complementary DNA
CI	mitochondrial respiratory chain complex I
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria For Adverse Events
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
[redacted]	[redacted]
GCL	ganglion cell layer
GCP	Good Clinical Practice
GGT/γGT	Gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GMO	genetically modified organism
HIV	human immunodeficiency virus
HVF	Humphrey Visual Field
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IMP	investigational medicinal product

IOP	intra-ocular pressure
IPL	inner plexiform layer
IRB	Institutional Review Board
IRS	interactive response system
IVT	intravitreal
LHON	Leber Hereditary Optic Neuropathy
LogMAR	Log of the minimal angle of resolution
MD	mean deviation
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
mtDNA	mitochondrial deoxyribonucleic acid
NADH	reduced nicotinamide adenine dinucleotide
ND4	NADH dehydrogenase 4
NHP	Non-Human Primate
OCT	optical coherence tomography
[redacted]	[redacted]
qPCR	quantitative polymerase chain reaction
rAAV2/2	recombinant adeno-associated viral vector, serotype 2
RGC	retinal ganglion cell
RNFL	retinal nerve fiber layer
SAE	serious adverse event
SD-OCT	spectral domain optical coherence tomography
[redacted]	[redacted]
SOP	Standard Operating Procedure
SUN	Standardization of Uveitis Nomenclature
TEAE	Treatment-Emergent Adverse Event
[redacted]	[redacted]
WHO	World Health Organization

2 STUDY OBJECTIVES

2.1 Primary

To evaluate the efficacy of GS010 compared with sham at Week 48 in the change from baseline of the Log of the minimal angle of resolution (LogMAR) in subjects affected for 6 months or less by LHON.

2.2 Secondary

- To evaluate the efficacy of GS010 compared with sham over the follow-up period and at Week 96 in the change from baseline of the LogMAR.
- To verify whether the efficacy at Week 48 and at Week 96 of GS010 compared with sham and measured by the change from baseline in the LogMAR is dependent upon the treatment of the better- or the worse-seeing eye.
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- To assess the effect of GS010 on parameters measured with high resolution SD-OCT.
- To assess the effect of GS010 on visual fields obtained with the Humphrey Visual Field (HVF) Analyzer II.
- To assess the effect of GS010 on contrast sensitivity measured with the Pelli-Robson chart.
- To assess the effect of GS010 on color vision measure with the Farnsworth-Munsell 100 Hue color test.

[redacted]

2.4 Safety

- To assess the safety and tolerability of GS010.

[redacted]

3 STUDY ENDPOINTS

3.1 Primary

The primary endpoint will be the ETDRS visual acuity (quantitative score) at Week 48 after IVT injection. The subjects' LogMAR scores, which are derived from the number of letters they read on the ETDRS chart, will be used for statistical analysis purposes. The change from baseline in each eye will be the primary response of interest.

3.2 Secondary

- ETDRS visual acuity (quantitative score) over the follow-up period and at Week 96 after IVT injection. Change from baseline of the LogMAR scores will be used for statistical analysis purposes.
- Response status to treatment at Week 48 and 96 after IVT injection. Responder will be defined by an improvement of at least 15 letters in the visual acuity score obtained with ETDRS *or* being greater than a Snellen acuity equivalent of 20/200.
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- Measure of contrast sensitivity with the Pelli-Robson chart at Week 48 and Week 96.
- Measure of color vision with the Farnsworth-Munsell 100 Hue color vision test at Week 48 and Week 96.

[redacted]

3.4 Safety

- Adverse events (AEs) and serious adverse events (SAEs), including those that are treatment-emergent and non-treatment-emergent, throughout the study period and at each study visit. Incidence and severity of systemic and local (ocular) AEs and SAEs will be determined at each clinical site and for the entire study cohort.

[redacted]

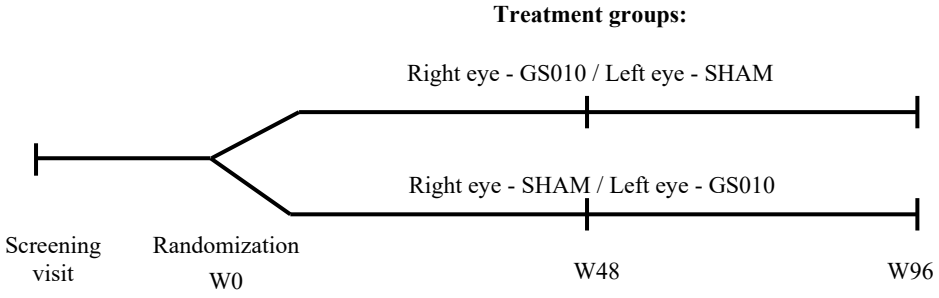
4 STUDY PLAN

4.1 Study Design

GS-LHON-CLIN-03A is a Phase III double-masked, sham-controlled, multicenter, multi-country, study. Recruitment is competitive.

Both eyes will receive standard antiseptic preparation, administration of topical local ocular anesthetic agents and will undergo pupillary dilation. Administration of an IOP lowering agent will precede treatment. GS010 will be administered once during the study via a single IVT injection. Sham IVT injection will be performed whereby pressure will be applied to the eye at the site of a typical procedure using the blunt end of a syringe without a needle.

The right eye of each subject will be randomly allocated to receive either GS010 or sham treatment in a 1:1 allocation ratio. The fellow (left) eye will receive the treatment not allocated to the right eye. Therefore, each subject will receive GS010 in one eye and sham treatment in the fellow eye.



An algorithm with a testing hierarchy will be employed to determine the better- and worse-seeing eye of each subject prior to randomization. The randomization will be based on the right and left eye, because if the right eye is treated the left eye will receive sham and vice versa the treatment groups will be automatically balanced. However, the better- or worse-seeing eye at entry can be a confounding factor, and it cannot be discarded that the treatment effect will be the same in the better and worse seeing-eye. Secondarily, in order to verify this hypothesis, an adaptive randomization technique called Efron's minimization method will be used to minimize the imbalance of treatment groups between the better-seeing eyes treated and worse-seeing eyes treated.

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resolution of the AE or the determination that no further clinical evolution is expected. Centralized analysis of ETDRS, automated visual fields, SD-OCT, color vision and contrast sensitivity will be performed.

Trial visits:

The trial is divided into the following visits:

- Screening Visit (Visit 1): From 28 to 2 days before IMP administration.
  This visit will allow Investigators to assess subject eligibility based on selection and non-selection criteria.
- Inclusion Visit (Visit 2): 1 day before IMP administration.
  This visit will allow Investigators to confirm the subject's eligibility based on inclusion and exclusion criteria. Subjects will undergo baseline ophthalmological testing.
  After the subject is confirmed to be eligible for the study, the right eye will be randomized to GS010 or sham treatment based on a pre-defined central randomization scheme.
- Treatment Visit (Visit 3): Day of IMP administration.
  Subjects will receive GS010 by IVT injection according to the randomized treatment assigned. The fellow eye will receive the alternative treatment.
- Follow-up visits (Visits 4 to 12): Nine follow-up visits after-IVT procedure will be conducted at 24 hours and 2, 4, 8, 12, 24, 48, 72, and 96 weeks.

An overall schedule of events for the study is in Section 4.2.1. A schedule of events for Visits 3 and 4 (those visits that will be conducted by the unmasked study site team) are in Section 4.2.2.

A DSMB meeting will be convened at least every 6 months to review the safety data.

Study duration:

Initiation of the trial with the first subject's first visit is planned for late Q4 2015. The estimated recruitment period is 12 months and will be dependent on recruitment rate. Total study follow-up is 96 weeks and the study will end with the last subject's last visit. The last subject's last visit is estimated to occur late Q4 2018. Therefore, the estimated study duration is 3 years.

At the end of this initial study period, a long-term safety and efficacy study as detailed in a future separate protocol will be initiated for further evaluation of the safety and efficacy durability. The long-term safety study will be conducted according to current regulatory authority recommendation.

4.2 Schedule of Events

4.2.1 Overall Schedule of Events

Evaluation	Screening Visit	Inclusion Visit	Treatment visit	Study Follow-up Visits								
Visit	**1**	**2**	**3[1]**	**4[1]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 EOS[2]**
Week(s)	**-4 to -1**				**2**	**4**	**8**	**12**	**24**	**48**	**72**	**96**
Day(s)	**-28 to -2**	**-1**	**0**	**1**	**14 (±2D)**	**28 (±3D)**	**56 (±6D)**	**84 (±9D)**	**168 (±17D)**	**336 (±30D)**	**502 (±30D)**	**672 (±30D)**
Signed informed consent	X											
Selection/non-selection criteria	X											
Inclusion/exclusion criteria		X										
Demographics[3]	X											
Relevant medical and surgical history	X											
Prior medications	X											
[redacted]	[redacted]	[redacted]							[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]											[redacted]
Laboratory Assessments												
ND4 (G11778A) genotyping[7,8,]	X											
[redacted]	[redacted]							[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum HIV testing[8]	X[9]											
Pregnancy test (for women of childbearing potential)[8]	X[9]											
[redacted]		[redacted]			[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]				[redacted]		[redacted]	[redacted]	[redacted]		[redacted]
[redacted]		[redacted]			[redacted]							
Ocular Assessments												
Refraction for BCVA	X	X		X	X	X	X	X	X	X	X	X

Evaluation	Screening Visit	Inclusion Visit	Treatment visit	Study Follow-up Visits								
Visit	**1**	**2**	**3[1]**	**4[1]**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 EOS[2]**
Week(s)	**-4 to -1**				**2**	**4**	**8**	**12**	**24**	**48**	**72**	**96**
Day(s)	**-28 to -2**	**-1**	**0**	**1**	**14 (±2D)**	**28 (±3D)**	**56 (±6D)**	**84 (±9D)**	**168 (±17D)**	**336 (±30D)**	**502 (±30D)**	**672 (±30D)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETDRS visual acuity	X	X		X	X	X	X	X	X	X	X	X
Humphrey visual field 30-2	X	X		X	X	X	X	X	X	X	X	X
Spectral domain optical coherence tomography	X	X					X		X	X	X	X
Pelli-Robson contrast sensitivity	X	X		X	X	X	X	X	X	X	X	X
Farnsworth-Munsell 100 Hue color testing	X	X		X	X	X	X	X	X	X	X	X
Color Fundus Photos	X[13]			X[14]								
[redacted]				[redacted]								
[redacted]												
[redacted]		[redacted]							[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]							[redacted]	[redacted]	[redacted]	[redacted]
IMP												
IMP administration[16]			X									
Safety Assessments												
Concomitant medications	X											
AE and SAE assessment	X											

D = day; AE = adverse event; [redacted] ETDRS = Early Treatment Diabetic Retinopathy Study; [redacted] SAE = Serious adverse event; AAV2 = adeno-associated viral vector, serotype 2; EOS = end of study; ND4 = NADH dehydrogenase 4; BCVA = best corrected visual acuity; [redacted] IMP = investigational medicinal product.

1 Visits 3 and 4 will be conducted by the unmasked site team. A schedule of events for these visits is below.

2 Subjects who discontinue participation in the study prematurely (i.e. prior to Visit 12) will complete an end-of-study (EOS) visit including all procedures listed for Visit 12.

3 Includes gender and date of birth.

[redacted]

[7] All subjects will be required to have a blood sample taken for genotyping analysis by the central study laboratory. Subjects with previously documented G11778A *ND4* mitochondrial mutation can proceed to visit 2 without the results of the central laboratory genotyping. Subjects without previously documented G11778A *ND4* mitochondrial mutation will be required to have the results of the central laboratory genotyping available for Visit 2.

[redacted]

[10] [redacted]

[11] At Visit 3, baseline assessments should be done 60-120 minutes prior to IVT injection.

[12] [redacted]

[13] Obtained as baseline for future comparison if necessary.

[14] Obtained only if necessary for grading ocular inflammation.

[redacted]

[16] Via intravitreal injection with fellow-eye sham IVT procedure.

[17] [redacted]

4.2.2 Schedule of Events to be conducted by the Unmasked Site Team

Evaluation	**Treatment Visit**					**Follow-up Visit**
Visit	**3**					**4**
Day(s)	**0**					**1**
Hour(s)	**0**	**0.5**	**1**	**2**	**4**	
[redacted]						
Refraction for best corrected visual acuity						X
[redacted]						
[redacted]						
ETDRS visual acuity						X
Humphrey visual field 30-2						X
Pelli-Robson contrast sensitivity						X
Farnsworth-Munsell 100 Hue color vision testing						X
Color Fundus Photos						X[9]
Investigational medicinal product (IMP) administration[7]	X					
Concomitant medications	X					
AE and SAE assessment[10]	X					
[redacted]						

AE = adverse event; ETDRS = Early Treatment Diabetic Retinopathy Study; SAE = Serious adverse event; AAV2 = adeno-associated viral vector, serotype 2; IOP = intra-ocular pressure; [redacted]

[redacted]

3 [redacted]

5 ±15 minutes
6 ±30 minutes
7 Via intravitreal injection with fellow-eye sham procedure.
8 Before and after pupil dilation.
9 Obtained only if necessary for grading ocular inflammation.
10 Ocular AEs commencing at Visit 3 or Visit 4 will be followed in a focused manner by the unmasked study team at subsequent visits until resolution or the determination that no further clinical evolution will occur.

[redacted]

[redacted]

5 POPULATION

The study population will include subjects with LHON due to the G11778A *ND4* mutation with loss of vision in at least one eye for ≤180 days in duration.

5.1 Number of Subjects

It is planned that approximately 40 subjects will be screened in order to randomize 36 into the study at 7 sites (one each in France, Germany, Italy, and the United Kingdom and 3 in the United States).

5.2 Selection for the Study

5.2.1 Selection Criteria

Subjects must meet all the following criteria at the Screening Visit (Visit 1) in order to be included into the study.

1. Age 15 years or older.
2. Onset of vision loss based on medically documented history or subject testimony, in at least one eye for ≤180 days in duration and if both eyes are affected the duration of vision loss in both eyes must be ≤180 days in duration.
3. Each eye of the subject maintaining visual ability to allow at least for counting of the examiner's fingers at any distance.
4. Female subjects (if of childbearing potential) must agree to use effective methods of birth control up to 6 months after IVT injection and male subjects must agree to use condoms for up to 6 months after IVT injection.
5. Ability to obtain adequate pupillary dilation to permit thorough ocular examination and testing.
6. Signed written informed consent.

5.2.2 Non-Selection Criteria

Subjects who meet at least one of the following criteria at the Screening Visit (Visit 1) will not be included into the study.

1. Any known allergy or hypersensitivity to GS010 or its constituents.
2. Contraindication to IVT injection.
3. IVT drug delivery to either eye within 30 days prior to the Screening Visit (Visit 1).
4. Previous vitrectomy in either eye.
5. Narrow angle in either eye contra-indicating pupillary dilation.
6. Presence of disorders of the ocular media, such as the cornea and lens, which may interfere with visual acuity and other ocular assessments during the study period.
7. Vision disorders, other than LHON, involving visual disability or with the potential to cause further vision loss during the trial period.
8. Causes of optic neuropathy other than LHON and glaucoma.

9. Subjects with known mutations of other genes involved in pathological retinal or optic nerve conditions.
10. Presence of ocular or systemic disease, other than LHON and well-controlled glaucoma, whose pathology or associated treatments might affect the retina or the optic nerve.
11. History of amblyopia associated with a Snellen visual acuity equivalent of worse than 20/80 (equivalent to 6/24 at 6 meters, decimal acuity 0.25, LogMAR +0.6) in the affected eye.
12. Presence of ocular conditions, which in the opinion of the Investigator will prevent good quality SD-OCT imaging from being obtained.
13. Presence, in either eye, of uncontrolled glaucoma, defined as an IOP greater than 25 mmHg, despite maximal medical therapy with IOP-lowering agents.
14. Active ocular inflammation or history of idiopathic or autoimmune-associated uveitis.
15. Subjects participating in another clinical trial and receiving an IMP within 90 days prior to the Screening Visit (Visit 1).
16. Previous treatment with an ocular gene therapy product.
17. Subjects who have undergone ocular surgery of clinical relevance (per Investigator opinion) within 90 days preceding the Screening Visit (Visit 1).
18. Female Subjects who are or who intend to breast feed during the trial period.

5.3 Inclusion Criteria

Subjects included in the study must satisfy all the following criteria at the Inclusion Visit (Visit 2).

1. Documented results of genotyping showing the presence of the G11778A mutation in the *ND4* gene and the absence of the other primary LHON-associated mutations (*ND1* or *ND6)* in the subject's mitochondrial DNA.
2. Review of all selection criteria to ensure continued compliance. For Selection Criterion 2, the vision loss duration should only be calculated based on the Visit 1 date.
3. Have a negative test for infection with human immunodeficiency virus (HIV).
4. Have a negative pregnancy test for women of childbearing potential (a woman who is two years post-menopausal or surgically sterile is not considered to be of childbearing potential).

5.4 Exclusion criteria

Subjects who meet at least one of the following criteria at the Inclusion Visit (Visit 2) will not be included in the study.

1. Any non-selection criteria which may have appeared after the screening visit.
2. Subjects taking idebenone who have not completely discontinued the idebenone at least 7 days prior to Visit 2. If the subject has not discontinued idebenone at least 7 days prior to Visit 2, the visit may be delayed until the 7-day period is complete.
3. Presence, at the time of study inclusion, of infectious conjunctivitis, keratitis, scleritis or endophthalmitis in either eye.

4. Presence of systemic illness, including alcohol and drug abuse (except nicotine), or medically significant abnormal laboratory values that are deemed by the Investigator to preclude the subject's safe participation in the study.
5. Presence of illness or disease that, in the opinion of the Investigator, include symptoms and/or the associated treatments that can alter visual function, for instance cancers or pathology of the central nervous system.
6. Any medical or psychological condition that, in the opinion of the Investigator, may compromise the safe participation of the subject in the study or would preclude compliance with the study protocol or ability of the subject to successfully complete the study.
7. Subjects unable or unwilling to comply with the protocol requirements.

5.5 Deviation from Inclusion/Exclusion Criteria

No protocol deviation related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be allowed prospectively.

6 STUDY CONDUCT

6.1 Study Procedures by Time Point

6.1.1 Visit 1 – Screening Visit

The following procedures will be conducted at the Screening Visit (Visit 1), 28 to 2 days before the Treatment Visit (Visit 3):

- Informed consent read, understood, and signed. If the subject is unable to read the informed consent document, presence of an impartial witness is required to confirm that the contents of the document were explained to the subject. The impartial witness must sign the informed consent form (ICF). The subject must always be asked to sign or mark the ICF regardless of their vision ability.
- Assess subject eligibility for the study with regard to selection and non-selection criteria. If the subject fails to meet any of these criteria, the subject will not be selected for study participation and no further assessments will be conducted.
- Collection of subject demographics (gender, date of birth), relevant medical and surgical history, and relevant prior medications.
- [redacted]
- Blood draw for serum pregnancy test for women of childbearing potential. Testing will be conducted at the central laboratory unless it is determined that the results will not be received from the central laboratory in time for Visit 2, in which case a local laboratory may be used. The results of this test must be available and documented at Visit 2.
- Blood draw for genotyping to confirm the presence of the G11778A mutation in the mitochondrial *ND4* gene. All subjects will be required to have a blood sample taken for genotyping analysis by the central study laboratory. Subjects with previously documented G11778A *ND4* mitochondrial mutation can proceed to visit 2 without the results of the central laboratory genotyping. Subjects without previously documented G11778A *ND4* mitochondrial mutation will be required to have the results of the central laboratory genotyping available for Visit 2.
- [redacted]
- Blood draw for serum HIV testing. Testing will be conducted at the central laboratory unless it is determined that the results will not be received from the central laboratory in time for Visit 2, in which case a local laboratory may be used. The results of this test must be available and documented at Visit 2.

- Refraction for best corrected visual acuity (BCVA) performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- HVF 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photography after pupil dilation.
- Recording of concomitant medications, including supplements.
- Recording of AEs and SAEs.

6.1.2 Visit 2 – Inclusion Visit

The following procedures will be conducted at the Inclusion Visit (Visit 2), the day before IMP administration:

- Assess subject eligibility for the study with regard to inclusion and exclusion criteria. If the subject fails to meet any of these criteria, the subject will be excluded and no further assessments will be conducted.
- [redacted]
- Review of laboratory results to confirm subject's eligibility.
- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- HVF 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- [redacted]
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.
- Recording of AEs and SAEs.

6.1.3 Visit 3 - Treatment Visit

The following procedures will be conducted at the IMP Administration Visit on Day 0 (Visit 3). ***All Visit 3 procedures will be performed by the unmasked study team. A schedule of events for the unmasked site team is in Section 4.2.***

The following procedures will be performed 60-120 minutes prior to IMP administration:

- [redacted]
- Administration of IOP lowering agent.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.
- Recording of AEs and SAEs.

After these procedures are complete, pupil dilation, local anti-sepsis, topical anesthesia, GS010 administration, and sham procedures will be performed per the IVT and Sham Procedure Guide.

Following IVT injection, the following procedures will be conducted:

- [redacted]
- Recording of any new AEs and SAEs.
- Recording of any new changes or additions to concomitant medications and any new changes in concomitant medication dose or regimen, including supplements, after IVT injection.

6.1.4 Follow-up Visits

6.1.4.1 Visit 4 – Day 1

The following procedures will be conducted on Day 1 (Visit 4), the day following IMP administration. ***All Visit 4 procedures will be performed by the unmasked study team. A schedule of events for the unmasked site team is in Section 4.2.***

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation. This assessment will be for safety purposes only and will not be analyzed as efficacy data.

- HVF 30-2 testing performed prior to pupil dilation. This assessment will be for safety purposes only and will not be analyzed as efficacy data.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation. This assessment will be for safety purposes only and will not be analyzed as efficacy data.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation. This assessment will be for safety purposes only and will not be analyzed as efficacy data.
- Color fundus photos if necessary for grading ocular inflammation.
- Collection of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.2 Visit 5 – Week 2

The following procedures will be conducted at Week 2 (Visit 5, ±2 days) following IMP administration:

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.3 Visit 6 – Week 4

The following procedures will be conducted at Week 4 (Visit 6, ±3 days) following IMP administration:

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.

- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.4 Visit 7 – Week 8

The following procedures will be conducted at Week 8 (Visit 7, ±6 days) following IMP administration:

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.5 Visit 8 – Week 12

The following procedures will be conducted at Week 12 (Visit 8, ±9 days) following IMP administration:

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.

- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.6 Visit 9 – Week 24

The following procedures will be conducted at Week 24 (Visit 9, ±17 days) following IMP administration:

- Refraction for BCVA performed prior to pupil dilation.
- 
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.7 Visit 10 – Week 48

The following procedures will be conducted at Week 48 (Visit 10, ±30 days) following IMP administration:

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.8 Visit 11 – Week 72

The following procedures will be conducted at Week 72 (Visit 11, ±30 days) following IMP administration:

- [redacted]
- Refraction for BCVA performed prior to pupil dilation.
- [redacted]
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.1.4.9 Visit 12 – Week 96 (or End of Study Visit)

The following procedures will be conducted at Week 96 (Visit 12, ±30 days, or end of study visit) following IMP administration:

[redacted]

- Refraction for BCVA performed prior to pupil dilation.
- [redacted].
- ETDRS visual acuity testing performed prior to pupil dilation.
- Humphrey Visual Field 30-2 testing performed prior to pupil dilation.
- SD-OCT performed after pupil dilation.
- Pelli-Robson contrast sensitivity testing performed prior to pupil dilation.
- Farnsworth-Munsell 100 Hue color vision test performed prior to pupil dilation.
- Color fundus photos if necessary for grading ocular inflammation.
- Recording of AEs and SAEs.
- Recording of any changes and additions to concomitant medications and any changes in concomitant medication dose or regimen, including supplements.

6.2 Premature Discontinuation

Subjects who discontinue participation in the study prematurely (i.e. prior to Visit 12) will complete an end-of-study visit including all procedures listed for Visit 12.

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

- Subject's request at any time for any reason.
- Physician's determination that subject's further participation in the protocol is not in the subject's best interest.
- The Sponsor's decision.
- Health Authorities' decision.

For any discontinuation, the Investigator will obtain all the required details and document the date of and the reason for the discontinuation in the case report form (CRF). If possible, Week 48 ETDRS visual acuity should be obtained.

If the reason for withdrawing from the study is an AE, the specific event will be recorded in the CRF.

6.3 Unscheduled Visits

Unscheduled visits may be performed anytime during the study to assess or follow up adverse events, at the subject's request, or at the request of the investigator. The date and reason for the unscheduled visit should be recorded in the source documentation.

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

- Any AEs.
- Reason for unscheduled visit.
- 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.

6.4 Additional Care of Subjects

Subjects who complete the study through Visit 12 (96 weeks of follow-up) will be offered participation in a long-term safety and efficacy study as detailed in a separate protocol that will be initiated for further evaluation of the safety and efficacy durability. The long term safety study will be conducted according to current regulatory authority recommendation.

7 DESCRIPTION OF STUDY PROCEDURES

7.1 Informed Consent

Prior to entering the study, the Investigator will explain to each subject (and the subject's parent/legal guardian if the subject is under the legal age of consent) the nature of the study, its purpose, procedures, expected duration, alternative therapies available, and the benefits and risks involved in study participation.

If the subject is of the legal age of consent, they will be given the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF to review and the opportunity to ask questions. The subject will be informed of their right to withdraw from the study at any time without prejudice. The subject should be able to answer simple questions about the study after the ICF has been reviewed and explained. After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and date the ICF to indicate the desire to participate in the study. If the subject is unable to read the informed consent document, presence of an impartial witness is required to confirm the contents of the document were explained to the subject. The impartial witness must sign the ICF. The subject must always be asked to sign or mark the form regardless of their vision. The Investigator will also sign and date the ICF. The time (hour and minute) the consent is signed must also be recorded by the subject or legal guardian and the person providing consent to the subject. Prior to participation in the study, the subject will receive a copy of the signed and dated consent form along with an emergency card with contact information for the Investigator and clinical facility staff in the event of a medical emergency during the trial.

If the subject is under the legal age of consent, the potential subject's parent or legal guardian will be given IRB/IEC-approved ICF to review and the subject will be given an IRB/IEC-approved pediatric assent form. Both the subject and the parent/legal guardian will be given the opportunity to ask questions. Both the subject and their parent/legal guardian will be informed of the subject's right to withdraw from the study at any time without prejudice. The subject and their parent/legal guardian should be able to answer simple questions about the study after the ICF and assent form have been reviewed and explained. After this explanation and before any study-specific procedures have been performed, the parent/legal guardian will voluntarily sign and date the ICF to indicate their informed consent for the subject to participate in the study. The subject will sign and date the pediatric assent form to indicate their desire to participate in the study. The Investigator will also sign and date the ICF and assent form. The time (hour and minute) the consent and assent are signed must also be recorded by the subject (on the assent form), the parent/legal guardian (on the ICF), and the person providing consent/assent (on both forms). Prior to participation in the study, the subject's parent/legal guardian will receive copies of the signed and dated consent and assent forms along with an emergency card with contact information for the Investigator and clinical facility staff in the event of a medical emergency during the trial.

7.2 Demographics and Other Clinical Evaluations

7.2.1 Demographics, Medical History, and Prior Medications

After subjects have signed an ICF for the purpose of this study, each subject's comprehensive medical history will be recorded, including medical and demographic information (according to national data collection regulations). All prior medications including prescription and non-prescription medications and preparations and health and/or dietary supplements taken by the subject within the previous 30 days will also be recorded. In addition, hospitalizations in the past 3 months and the reason for admission (medical/surgical/psychiatric/other) in the past 3 months will also be recorded.

7.2.2 Pregnancy Testing

Blood samples for serum pregnancy testing will be collected at the Screening Visit (Visit 1) for women of childbearing potential. Testing will be conducted at the central laboratory unless it is determined that the results will not be received from the central laboratory in time for Visit 2, in which case a local laboratory may be used. The results of this test must be available and documented at Visit 2. Samples will be handled according to a standardized procedure. This procedure will be provided to the Investigator centers prior to study start. Subjects with positive pregnancy tests will be excluded from study participation.

7.2.3 Virology

Blood samples for HIV testing will be collected at the Screening Visit (Visit 1). Testing will be conducted at the central laboratory unless it is determined that the results will not be received from the central laboratory in time for Visit 2, in which case a local laboratory may be used. The results of this test must be available and documented at Visit 2. Samples will be handled according to a standardized procedure. This procedure will be provided to the Investigator centers prior to study start. Subjects with positive tests for HIV will be excluded from study participation.

7.2.4 ND4 (G11778A) Genotyping

All subjects will be required to have a blood sample taken at Visit 1 for genotyping analysis by the central study laboratory. Subjects with previously documented G11778A *ND4* mitochondrial mutation can proceed to visit 2 without the results of the central laboratory genotyping. Subjects without previously documented G11778A *ND4* mitochondrial mutation will be required to have the results of the central laboratory genotyping available for Visit 2. Samples will be handled according to a standardized procedure. The testing will be analyzed by the central laboratory. This procedure will be provided to the Investigator centers prior to study start. The presence of the G11778A *ND4* mitochondrial DNA mutation must be documented at Visit 2 (Inclusion Visit).

7.3 Ophthalmic Evaluations

Detailed descriptions of all the ophthalmic evaluations will be detailed in the Ophthalmic Evaluations Manual. A central reading center will be used in quality control and analysis as detailed per evaluation in the Ophthalmic Evaluations Manual.

7.3.1 Visual Acuity

Enrolled subjects will include those able to read letters on the ETDRS chart ("on-chart" subjects) and those unable to read letters on the ETDRS chart but able to count fingers of the examiner at a given distance ("off-chart" subjects). On-chart subjects will have visual acuity measured with the ETDRS chart and an ETDRS score will be calculated. On-chart subjects will also have a Snellen acuity obtainable from the number of lines read on the ETDRS chart.

Off-chart subjects included in the study must maintain the visual ability to allow them to count fingers of the examiner as per the selection criteria. Off-chart subjects will not have an ETDRS score or a Snellen acuity obtainable from the ETDRS chart. Snellen acuity will be obtained utilizing the measured distance at which the subject was able to count the fingers of the examiner and a standardized formula available at (Karanjia 2014):

http://www.countfingers.com/

The Snellen acuities of on-chart and off-chart subjects will be converted to LogMAR for statistical analysis. Snellen acuities will be transformed to LogMAR using the standard formula available at:

http://www.myvisiontest.com/logmar.php

Additionally, 1 ETDRS line is considered equivalent to 0.1 LogMAR.

The visual testing at Visit 4 will be conducted for safety purposes and will not be analyzed as efficacy data (see Section 7.6.3).

7.3.2 Refraction for Best Corrected Visual Acuity

BCVA is defined as the best visual acuity that can be achieved by a subject with vision correction (e.g. glasses or contact lenses). Refraction testing for BCVA will be conducted at the Screening Visit (Visit 1) and Inclusion Visit (Visit 2) and at each follow up study visit at which visual acuity testing is conducted.

7.3.3 Spectral Domain Optical Coherence Tomography

SD-OCT will be obtained with the Spectralis® OCT (Heidelberg Engineering). Parameters will be obtained for the optic nerve (retinal nerve fiber layer) 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.

7.3.4 Visual Field Assessment

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

7.3.5 Contrast Sensitivity

Assessment of the effect of IMP on contrast sensitivity will be measured with the Pelli-Robson chart.

7.3.6 Color Vision

Assessment of the effect of GS010 on color vision will be assessed using a Farnsworth-Munsell 100 Hue color vision test.

7.3.7 Color Fundus Photos

Color fundus photos will be obtained at Visit 1 to establish a baseline. Color fundus photos will be obtained at Visit 4 through Visit 12 as necessary when required for grading of vitreous inflammation.

[redacted]

[redacted]

7.5 Clinical Laboratory Tests

For any test abnormality deemed clinically significant, an AE should be recorded (unless the result was considered erroneous) and repeat analysis will be performed until resolution or until the Investigator determines that resolution of the laboratory abnormality is not expected.

[redacted]

[redacted]

7.5.5 Laboratory Results Review

[redacted]

It is the Investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the Investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the Investigator needs to ascertain if this is a clinically significant abnormal change from baseline for that individual subject.

[redacted]

[redacted]

7.7 Protocol Deviations

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

8 STUDY DRUG MANAGEMENT

8.1 Description of GS010

AAV is a small parvovirus that infects humans and other primate species. The vector used in this study is a recombinant form of the serotype 2 of the AAV2 vector, rAAV2/2, encoding the human *ND4* gene 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. The construct includes the cis-acting elements of the human *COX10* mRNA (mitochondrial targeting sequence 5' of the complementary DNA [cDNA], and the 3'untranslated region at the 3' end of the cDNA) ensuring the efficient mRNA targeting to mitochondria and delivery of the corresponding protein.

8.1.1 Formulation

GS010 (rAAV2/2-*ND4*) drug product is a sterile suspension of purified viral vector formulated in balanced salt solution (BSS) plus 0.001% Pluronic F68®. It is filled in vials and stored frozen at ≤ -70°C ready for intended medical use. Details on the preparation of GS010 IMP for administration to subjects are described in the Pharmacy Manual.

8.1.2 Storage

IMP is stored at ≤-70°C in a freezer under the supervision of the study pharmacist or the Investigator. The IMP vials will be dispensed only with the written authorization of the Investigator or his/her delegate that has been specifically designated to this study. After reconstitution (see Section 8.3), the IMP may be stored for up to 12 hours at 2 to 8ºC before injection.

GS010 IMP must be kept in a locked and restricted access storage facility.

8.2 Packaging and Labeling

GS010 IMP is individually packaged. The primary label on the vial as well as secondary container labeling is in the country-specific language for each site. The labels are compliant with local regulatory requirements. The primary and secondary packaging together comply with the labeling requirements.

Packaging of IMP will be compliant with the International Air Transport Association (IATA) regulation for genetically modified organisms.

GS010 IMP will be shipped on dry ice (with 1 probe for temperature monitoring during transport).

8.3 Dose and Administration

GS010 IMP reconstitution will be performed at the site pharmacy according to the reconstitution protocol described in the Pharmacy Manual. Reconstitution kits will be

supplied by the Sponsor. The Pharmacy Guide and the Guide for Intra-Vitreal Injection of GS010 (rAAV2/2-*ND4*) and Sham Procedures will describe all details for preparation and proper handling of GS010 IMP.

GS010 IMP will be administered on Day 0 (Visit 3) via a single IVT injection in one eye of each subject. The dose of GS010 to be administered is 9E10 vg/eye. The injection will be performed in the vitreous humor under local anesthesia. The volume of the injected formulation is 90 µL.

Sham IVT injection will be performed on the fellow eye (i.e. the one not randomized to receive GS010). Sham procedures will be performed by applying pressure to the eye at the location of a typical procedure using the blunt end of a syringe without needle.

IVT injection and sham procedures, including pre- and post-procedure steps, will be performed according to the Guide for Intra-Vitreal Injection of GS010 (rAAV2/2-*ND4*) and Sham Procedures.

8.4 Dispensing and Accountability

GS010 IMP will only be dispensed, according to Investigator's prescription, to eligible subjects who meet all selection and inclusion criteria and according to the treatment scheme.

GS010 IMP will be tracked during the handling process from prescription to destruction (through dispensation, reconstitution, administration and decontamination).

The Investigator or, depending on center organization, the Pharmacist or the person responsible for study medication management will keep an IMP accountability log detailing the dates, batch number and quantity dispensed for each subject.

Accountability records will be verified by the study monitor during site visits. All used and unused GS010 IMP vials will be recorded.

At the end of the study, all unused GS010 IMP vials will be destroyed at the investigation center following internal procedures for genetically modified organisms (GMOs). A copy of the certificate of destruction should be made available to the sponsor.

GS010 IMP accountability is ultimately the responsibility of the Investigators. This responsibility however may be delegated to the Hospital Pharmacists. This delegation will be documented in the Site Trial Master file.

8.5 Prior and Concomitant Therapy

Prior therapy is defined as prescription and non-prescription medications and preparations, including health and/or dietary supplements taken within 30 days prior to signing the informed consent, but discontinued prior to signing informed consent. Concomitant therapy is defined as prescription and non-prescription medications and preparations,

health and/or dietary supplements other than GS010 IMP that the subject receives during the course of the study (i.e. any time after the signing of informed consent). This includes any medication started prior to signing informed consent and continued after signing.

Idebenone must be completely discontinued for at least 7 days prior to Visit 2 and is prohibited throughout the study. If idebenone has not been discontinued at least 7 days prior to Visit 2 and if the study protocol timeframe between the visits is respected, Visit 2 may be delayed until the 7-day period is complete.

8.6 Method of Assigning Treatment

The right eye of each subject will be randomly allocated to receive either GS010 or sham treatment in a 1:1 allocation ratio. The fellow (left) eye will receive the treatment not allocated to the right eye. Therefore, each subject will receive GS010 in one eye and sham treatment in the fellow eye. Prior to randomization, each subject's better- and worse-seeing eye will be determined. Efron's minimization method will be used in the randomization process to balance as much as possible the two treatment groups (GS010 and sham) in the better-seeing eyes.

To enroll a subject (Visit 1), the Investigator will call an interactive response system (IRS) and provide brief details about the subject to be enrolled. Each subject will receive a subject number assigned at screening, which will serve as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator (or designee) and the IRS regarding a particular subject. Subject numbers will be tracked via the IRS.

To randomize a subject (Visit 2), the masked Investigator (or designee) will call the IRS and provide brief details about the subject to be randomized. Eligible subjects will be randomized in a 1:1 ratio (right/left eye), taking into account the Efron's minimization method, using the IRS.

The IRS User Guide will describe the steps of the randomization process from the subject's screening up to before IVT injection.

An algorithm with a testing hierarchy will be employed prior to randomization to determine the better- and worse-seeing eye of each subject, as follows:

1. ETDRS visual acuity score for subjects able to read the ETDRS chart. The eye with the higher ETDRS score is the better-seeing eye. For subjects who cannot read the ETDRS chart ("off chart" subjects) a standard study procedure will be used to determine visual acuity based on counting fingers at a given distance. The eye with the best visual acuity based on this method is the better-seeing eye. If one eye of a subject is able to read letters on the ETDRS chart and one eye cannot, the eye able to read the ETDRS chart is the better-seeing eye.
2. SD-OCT parameters (to be used if there is no inter-eye difference based on Criterion 1):

i. The initial SD-OCT parameter will be the total volume of the RGC layer of the macula. The better-seeing eye will have the greater volume and quadrant thickness, unless there is macula edema. A difference of ≥5% is considered significant to determine greater volume.

ii. The second SD-OCT parameter (to be used if there is no inter-eye difference in criteria 2i) will be the combined volume of the RGC layer of the inner and outer nasal quadrants of the macula. The better-seeing eye will be the eye with greater volume. A difference of ≥5% is considered significant to determine greater volume.

3. Contrast sensitivity measured with the Pelli-Robson chart (to be used if there is no inter-eye difference in criteria 1 or 2). The eye with the best Log CS (contrast sensitivity) score is the better-seeing eye.

8.7 Masking

Masking will be accomplished with sham injection. Sham IVT injection will be performed by applying pressure to the eye at the location of a typical procedure using the blunt end of a syringe without a needle. Thus treatment allocation will be double-masked. The subject will remain masked at all times during the study. An unmasked team at the site will perform all procedures at Visit 3 and Visit 4 and focused follow up of ocular AEs commencing at Visits 3 and 4 until resolution of the AE or the determination that no further clinical evolution is expected. The unmasked team includes the injecting investigator(s), allied medical professionals who assist with IVT injection and ophthalmic technicians/optometrists who perform vision testing at Visit 4. The unmasked team will enter eye-related AEs identified at Visits 3 and 4 into the CRF in a masked way. A masked team at the site will conduct all other study procedures. A schedule of events for the unmasked site team is in Section 4.2.

Unmasked individual pharmacovigilance CRO personnel may know the treatment allocation of a given subject. No Sponsor or CRO personnel in charge of the conduct of the study (e.g. CRA, data manager, study manager etc.) will have access to treatment information.

8.8 Procedure for Unmasking

The treated/untreated eye information (GS010-treated eye versus sham-treated eye) should not be unmasked unless knowledge of the subject's eye treatment is required for the subject's clinical care and safety. The Investigator/clinical masked team will be provided with instructions to allow them to unmask the treatment via IRS. In the unlikely event that knowledge of the eye treatment assignment is necessary in order to care for a subject, the Investigator may decide to unmask the treatment allocation for safety reasons. If the eye treatment is unmasked, the Sponsor and the assigned Clinical Research Associate (CRA) must be notified within 24 hours. Documentation of unmasking should be recorded in the subject's medical record with the reason for unmasking, the date and time of the unmasking, and the names of the personnel involved.

9 ADVERSE EVENTS

The condition of the subject will be monitored throughout the study. Overall incidence of AEs and SAEs will be evaluated for the study as a whole.

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any event or laboratory abnormality that leads to a medical intervention, including withdrawal of IMP or significant additional concomitant therapy, will be considered an AE. Worsening of visual acuity determined by the Investigator to be due to progression of LHON will not be considered an AE.

AEs should be volunteered by the subject, be observed from examination of the subject at a clinic visit, or be from observations of clinically significant laboratory values or special examination abnormal values. AEs will not be solicited by the use of a specific list of anticipated events.

All AEs are to be assessed and recorded in a timely manner. Each AE is to be documented with reference to severity, date of occurrence, duration, treatment, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. In addition, the Investigator must assess whether the AE is drug-related or not. Changes in severity of AEs and resolution dates should be documented as separate events.

AEs will be captured from the first study-related procedure through to the completion of the protocol-defined safety follow-up as defined in Section 9.5 and Section 10.3.

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.

Intermittent AEs will not be reported as multiple AEs. The definition of an intermittent AE is "a recurring event with the same severity, frequency, and causality."

Clinically relevant abnormal findings observed during vital signs measurements or physical examinations will be reported as AEs.

9.1 Reporting and Documentation of Adverse Events

9.1.1 Reporting

At each visit, any AE directly observed or mentioned by the subject will be reported by the Investigator or designee on the page "Adverse Events" of the CRF (also called the "AE page"). The unmasked team will report AEs commencing at Visits 3 and 4 and the masked team will document AEs commencing at all other visits. The unmasked team will enter

eye-related AEs identified at Visits 3 and 4 into the CRF in a masked way and will perform focused follow up at subsequent visits of ocular AEs commencing at Visit 3 and Visit 4 until AE resolution or the determination that no further clinical evolution will occur. The following items must be documented:

Nature of the event with self-explanatory and concise medical terminology (indicate a diagnosis or syndrome instead of symptoms).

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).

- Severity.
- Relationship to IMP.
- Relationship to study procedure.
- Outcome.
- Seriousness.
- Action taken regarding the IMP.
- 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).

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.

9.1.1.1 Assessment of Severity

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

Should an event be missing in one of the scales, the following 3 point scale is 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.

The correspondence between the two scales is as follows:

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

9.1.1.2 Relationship to IMP and/or Procedures

The relationship of each AE to IMP and/or study procedures will be evaluated as follows:

- Unrelated: There is evidence of relationship to a cause other than the IMP/procedure. Does not meet criteria listed under unlikely, possible or probable.
- Unlikely: Does not follow a reasonable temporal sequence from administration. Is most likely produced by the subject's clinical state or by environmental factors or other therapies administered.
- Possible: Follows a reasonable temporal sequence from administration. Is not likely produced by the subject's clinical state or by environmental factors or other therapies administered.
- Probable: Follows a reasonable temporal sequence from administration. Clear-cut temporal association with IMP.

9.1.1.3 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 the 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 on the AE page in the CRF.

9.1.2 Documentation

AEs will be reported in the source document with at least the nature, the start date and the treatment (if applicable) of the event.

9.2 Ocular Inflammation

Specific assessment and documentation of ocular inflammation will be required. Ocular inflammation is an expected event based on preclinical NHP studies of GS010 and Phase I evaluation of GS010 in GS-LHON-CLIN-01. Specific, 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; (2) grading scheme for anterior chamber cells; (3) grading scheme for anterior chamber flare; and (4) activity of

uveitis terminology (for clinical evolution) (Jabs 2005). Investigators will grade cases of ocular inflammation according to these scales. These scales are provided in Table 1, Table 2, Table 3, Table 4, and Table 5 below.

Table 1 Anatomic Classification of Uveitis (SUN Working Group)

Type	Primary Site of Inflammation[a]	Includes
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	

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

Table 2 Grading Scheme for Anterior Chamber Cells (SUN Working Group)

Grade	Cells in Fluid[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 3 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 4 Activity of Uveitis Terminology (SUN Working Group)

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

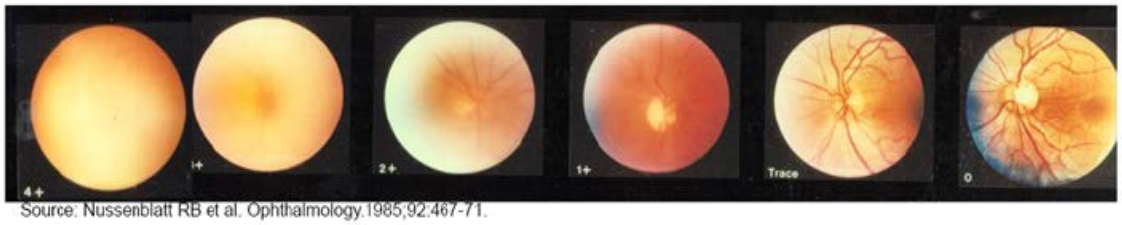
SUN = Standardization of Uveitis Nomenclature
[a] Applies to anterior chamber inflammation.

Grading of 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 utilized for anterior chamber cells (Table 2).

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 for all subjects. Color fundus photos will be obtained at subsequent visits when needed for grading of vitreous inflammation. The National Institutes of Health grading system (Nussenblatt 1985) will be used to grade the vitreous haze on the fundus photo. Table 5 and photos will serve as the basis for vitreous haze grading:

Table 5 National Institutes of Health Grading System for Vitreous Haze

Grade	Amount of Vitreous Flare/Haze
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;92:467-71.

9.3 Clinical Laboratory Changes

A laboratory abnormality is reported as an AE if it is out of range, considered by the Investigator as clinically significant (i.e. with clinical manifestations or requiring treatment or clinical management) and confirmed by a repeat measurement (if relevant). Worsening of laboratory parameters from pre-drug administration state will be considered on the same basis.

9.4 Concomitant Medication Assessments

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 CRF. During the study, any medication taken by the subject is to be reported by the subject and noted on the subject's source document and CRF. Any changes in concomitant therapy during the study will be documented, including cessation of therapy, initiation of therapy, and dose changes.

9.5 Adverse Event Follow-up

AEs occurring during the course of the study must be followed until resolution or the last visit planned by the protocol. AEs not resolved by the last visit planned by the protocol will be listed in the CRF as continuing/not resolved.

Subjects who experience the onset of an AE thought to be related to IMP after their final visit (Visit 12 or the end of study visit) will be followed up 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. SAEs thought to be related to IMP occurring after the final visit (Visit 12 or the end of study visit) must be reported as described in Section 10.3.

9.6 Pregnancy

If a female subject or the partner of a male subject believes she is pregnant (e.g., missed period, self-administered pregnancy test) the subject will be instructed to return to the clinical unit within 48 hours to undergo a serum pregnancy test. All confirmed pregnancies that occur within this study will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

If the pregnancy is confirmed before the subject receives IMP, the subject will be excluded from study participation and will not receive IMP.

Pregnancy (without associated unexpected or adverse sequelae) is not a reportable AE but must be reported to the Sponsor within 24 hours of the Investigator or study staff first becoming aware of the subject's condition.

10 SERIOUS ADVERSE EVENTS

10.1 Definition of Serious Adverse Event

A SAE is any AE that meets any of the following criteria:

- Results in Death.
- Is Life-threatening.
- Requires Inpatient hospitalization or prolongation of existing hospitalization.
- Results in Persistent or significant disability/incapacity.
- Is a Congenital anomaly/birth defect in the offspring of a subject who received IMP.

Other important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias.
- Convulsions that do not result in inpatient hospitalization.

10.2 Definition of Terms

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 if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug induced hepatitis can be fatal.

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. If anything untoward is reported during the procedure, that occurrence 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.

10.3 Reporting Serious Adverse Events

Any SAE occurring during the course of a study, i.e. between signature of the ICF and the end-of-study visit, irrespective of the treatment received by the subject MUST be reported to the Sponsor or their representative. The Investigator must complete and 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 faxed to the Sponsor or their designee immediately.

The SAE form must be completed in English.

10.3.1 Follow-up

If follow-up information is not available at the time of the event, this information must be forwarded to the Sponsor or their designee within one day of knowledge. The Sponsor or their designee may request information as needed.

10.3.2 Post-Study Serious Adverse Events

Any SAE occurring after the end of study visit and that is considered by the Investigator to be possibly or probably related to the IMP must be reported to the Sponsor or their designee as described above.

If the end of study visit is performed less than 28 days after IVT injection, ALL SAEs occurring between the end of study visit until 28 days after IVT injection will be reported to the Sponsor or their designee, regardless of their relationship to the IMP.

10.3.3 Notification to Regulatory Authorities/Gene Therapy Bodies/IRBs/IECs

The Sponsor or their designee is responsible for notifying serious and unexpected AEs to Health Authorities and to IRBs/IECs in accordance with local law.

Gene Therapy Bodies will be informed as locally required.

10.3.4 Information to Investigator

When an SAE has been reported to Health Authorities, the Sponsor or their designee will inform all other Investigators working in this study as well as those working with GS010 in other studies in accordance with local laws and regulations.

10.3.5 Documentation

All SAEs will be reported on the AE pages of the CRF using the same information as documented on the SAE form and in source documents. Copies of SAE forms will be filed in the Investigator Site File along with copies of any correspondence with the IRB/IEC. The Investigator Site File will also include copies of notification letters and/or faxes of forms sent to Health Authorities and Gene Therapy Bodies if appropriate.

11 QUALITY CONTROL AND ASSURANCE

11.1 Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigators and associated personnel before the study, and periodic monitoring visits by the Sponsor or their designee. Written instructions will be provided for study drug preparation and dosing, and collection, preparation, and shipment of blood samples. Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The Sponsor (or designee) will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the Sponsor (or designee). Any discrepancies will be resolved with the Investigator or suitably qualified designee, as appropriate.

11.2 Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines.

In accordance with the standards defined in Sponsor SOPs and applicable regulatory requirements, clinical studies sponsored by the Sponsor are subject to Sponsor Quality Audits at the study sites, which will be conducted by personnel from an appropriate unit. Site visit audits will be made periodically by the Sponsor's (or the CRO's) qualified compliance auditing team, which is an independent function from the study conduct team. Audits will include, but are not limited to, review of drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The Investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner. Full consultation with the Investigator will be made prior to and during such an audit, which will be conducted according to the Quality Assurance Unit SOPs. In addition, this study is subject to audit by regulatory authorities. If such a regulatory inspection occurs, the Investigator agrees to allow the regulatory inspector direct access to all relevant study documents. The Investigator should contact the Sponsor immediately if this occurs and must fully cooperate with the inspection conducted at a reasonable time in a reasonable manner.

12 STATISTICS

12.1 General Considerations

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 methodology to be used to address all study objectives. The SAP will also include formats for the summary and analysis tables, listings, and graphical displays.

GS-LHON-CLIN-03A (RESCUE) will include subjects affected for 180 days or less. Evidence indicates that improvement due to gene transfer therapy may be greatest at earlier stages of disease. This trial randomizes the right eye of each subject to receive GS010 or sham treatment in a 1:1 ratio and also uses the Efron's minimization method to balance as best as possible the treatment allocation to better- and worse-seeing eyes, as described in Section 8.6 for secondary analysis.

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 binary variables (responder analysis) will be presented by using counts and percentages. Least square (LS) means, 95% confidence interval and P-values will be reported derived from models and statistical tests.

12.2 Sample Size

Sample size calculation is based on the primary endpoint (LogMAR) and on the paired comparison of treated and sham eye. There is no published data regarding the within subject variance and the sample size calculation through paired comparison will therefore be very speculative for two reasons. The first reason is the within subject correlation between right and left eye and the second reason is the absence of information on the within and between subject variance of the LogMAR. Usually the within subject correlation is positive and the use of a null correlation is conservative. The absence of information on the LogMAR requires a second rough approximation of the mean and variance of LogMAR because the mean of ETDRS (Lam et al. 2014) is highly correlated to the variance of ETDRS ($R^2 = 0.839$ for the log-log relationship). This correlation is in favor of the use of the LogMAR to stabilize the variance but the transformation from ETDRS mean and variance to LogMAR mean and variance requires additional assumptions. Starting with a mean 23.4 and a standard deviation of 28.3 (Lam et al. 2014) and a difference of 20 letters on average between treated and sham eye, using the relationship between the log mean and the log variance obtained with Lam et al. (2014) results (log variance = 1.743 log mean + 0.48, $R^2 = 0.839$) and assuming a perfect lognormal distribution of ETDRS, the difference in means of the lognormal distributions is 0.65 (3.32 - 2.67) and the pooled standard deviation of the log distributions is 0.914. Assuming no correlation between both eyes, the within subject standard deviation is $(2x0.914^2)^{0.5} = 1.29$. The standardized difference in means is therefore 0.65/1.29 = 0.504 rounded to 0.50. The sample size required to get a power of 85% is exactly 36 subjects.

12.3 Analysis Populations

12.3.1 Intent-to-Treat Population

The intent-to-treat population will consist of all subjects who are randomized and receive study treatment (GS010 or sham treatment). This population will be the population for the primary efficacy analysis.

12.3.2 Safety Population

The safety population is defined as those subjects who received IMP. This population will be used as the population for all safety analyses.

12.4 Statistical Methods

12.4.1 Primary Analysis and Associated Planned Analyses

The primary analysis will be performed on the ITT subject population, which consists of all randomized and treated subjects. The change from baseline to Week 48 in the LogMAR acuity will be the primary response. The ETDRS score will not be directly used because there is a clear relationship between the mean and variance and according to Taylor's power law ($\log SD^2 = 1.743 \log \text{mean} + 0.48$, $R^2 = 0.839$) the best transformation is the logarithm (slope close to 2 and ease of interpretation of the difference in means of log). Because LogMAR is a logarithmic scale and is well known by ophthalmologists, this scale is retained as the primary one. The change from baseline of the treated eye will be compared to the change from baseline of the sham eye using a mixed model including the subject, the treatment and the baseline as covariates.

The center will not be included in the analysis as the number of subjects recruited per site will be very small. The difference in the mean change from baseline to Week 48 between the two treatment groups and associated 95% confidence interval will be reported. Alternative non parametric analysis (signed Wilcoxon test) will be performed as a sensitivity analysis to decrease the influence of possible outliers.

The treatment effect reflects well the effect on the better- and worse-seeing eye if no marked interaction between the eye status (better- versus worse-seeing) and treatment exists. To verify this hypothesis, a model including the subject as a random factor, the treatment as a fixed factor as well as the eye status (better- or worse-seeing) and the interaction between eye status and treatment will be fitted. If the P-value of the interaction test is below 0.15 a potential interaction is detected. In that case the better-seeing eye treated with GS010 will be compared to the better-seeing eye treated with sham and the worse-seeing eye treated with GS010 will be compared the worse-seeing eye treated with sham in an ANCOVA model including the LogMAR at baseline and the treatment. The study is then powered ($1-\beta = 0.8$) to detect a difference of approximately 30 letters between the two treatments.

A meta-analysis combining study GS-LHON-CLIN-03A (RESCUE) and study GS-LHON-CLIN-03B (REVERSE) is planned to verify whether the treatment effect at Week 48 as well as at Week 96 is dependent upon the time from onset of disease. If the treatment effect does not depend upon the eye status, a model using the change from baseline as the response, the subject as a random factor, the treatment as a fixed factor, the time from the onset of disease as a covariate and the interaction between the treatment and the time from the onset will be fitted. If the treatment effect is not the same in the better- and worse-seeing eye, a model will be fitted for the better-seeing eye and another model will be fitted for the worse-seeing eye. The subject factor will not be included in the model, but the LogMAR at baseline, the treatment, and the time from onset of disease will be included.

The generalizability of the treatment effect across countries will be addressed in the meta-analysis because the number of subjects per country could be sufficient to detect major heterogeneity.

12.4.2 Secondary Analysis

The treatment estimate at Week 96 will be based on the same statistical approach as the primary endpoint analysis. Another analysis will compare time course of the response up to Week 96 using the mixed model procedure. The responder analyses at both Week 48 and Week 96 will be based on a McNemar test for paired samples. To verify whether the treatment effect is dependent upon the better-seeing eye or the worse-seeing eye at study entry, a test of homogeneity of subgroups (better-seeing or worse-seeing eye treated) effects in stratified paired binary data (Zhao 2014) will be performed.

Like the primary endpoint, a meta-analysis will be performed combining both studies (GS-LHON-CLIN-03A (RESCUE) and study GS-LHON-CLIN-03B (REVERSE). A conditional logistic model will be used to assess the effect of better- and worse-seeing eye at study entry and the effect of time from onset of disease and the effect of treatment.

12.4.3 Analysis of Vision-Related Secondary Endpoints

SD-OCT will be presented by summary statistics for continuous data. Visual field data generated from HVF analyzer II, Goldmann applanation tonometry, color vision, and contrast sensitivity data will be summarized between the two treatments by using descriptive statistics.

[redacted]

12.4.5 Analysis of Safety

Incidence and severity of all treatment and non-treatment emergent local and systemic AEs and SAEs will be presented by system organ class and preferred term. Summary descriptive

statistics will be presented for all continuous variables. The visual testing at Visit 4 will be conducted for safety purposes and will not be analyzed as efficacy data (see Section 7.6.3).

All AEs will be coded using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA). Only AEs occurring after administration of IMP will be included in the safety analysis.

The incidence of AEs (number and percent of subjects reporting the AE at least once during the study) will be summarized by body system and preferred term for all AEs, by the Investigator's attribution of relationship to study drug and by severity. The details will be included in the statistical analysis plan.

12.4.5.1 Laboratory Data

At each visit where clinical laboratory assessments are conducted, summary statistics for the absolute laboratory value and the changes from baseline will be presented. Statistical testing will be performed at the Visit 12/end of study visit. Shift tables will be presented to compare the shifts between the baseline and post-baseline visits. Clinically significant abnormal lab values for different parameters will be summarized.

[redacted]

12.4.5.3 Other Variables Related to Safety

[redacted]

Concomitant medication verbatim terms on CRFs will be mapped to Anatomical Therapeutic Chemical Level 4 categories and Drug Reference Names using the World Health Organization (WHO) dictionary (Version December 1, 2006). Incidence (number and percent of subjects reporting the medication at least once during the study) will be summarized for all concomitant medications.

12.4.6 Demographic and Baseline Characteristics

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

12.5 Interim Analysis

No interim efficacy analyses are planned.

12.6 Timing of Primary Analysis

Primary endpoint analysis will be performed as soon as the last subject completes the Week 48 assessment and data are cleaned. At that point, all subjects will be recruited and followed for at least 48 weeks except in case of premature withdrawal. Many subjects will have reached Week 96 but not all of them. The study will be formally unmasked for the efficacy analysis at Week 48 to allow an early registration if results meet the expectations. The study will still continue up to scheduled end (Week 96). Although the study will have been unmasked for the study statistician, every effort (see Appendix V in Section 20.5) will be invested to maintain the masking of subjects and personnel in charge of the conduct of the study including study managers, data managers, CRAs, investigators (except international coordinating investigators per Appendix V in Section 20.5). After the completion of the study, only the analyses related to the Week 96 endpoints will be performed (see Appendix V in Section 20.5).

12.7 Handling of Missing Data

In case of missing data at Week 48, the following rules will be applied in the first imputation method:

Rule 1: If the LogMAR is available at the previous and the following visits then the imputed value at Week 48 will be a linear interpolation of LogMAR.

Rule 2: If there is no following visit due to drop out then the relative change (RC_i) from visit V_i to visit V_{i+1} will be calculated at each visit from the baseline to the visit preceding Week 48 in the group treated with a sham. The last available visit (V_i) with data (X_i) will be used as the starting time point. The imputed score at V_{i+1} for each eye will be equal to $X_{i+1} = X_i * RC_i$. The imputed score at the next missing visit V_{i+2} will be equal to $X_{i+2} = X_{i+1} * RC_{i+1}$, and so on up to Week 48 visit. The RC_i will be the same for the treated and sham eyes.

With the first method of imputation the between eye difference at Week 48 will be proportional to the between eye difference at the time of withdrawal because the same RC_i coefficients are used for both eyes.

The second imputation method leading to an additional sensitivity analysis will apply the same Rule 1 but Rule 2 will be based on the evolution of the difference between treated and sham eye. RC_i is then the relative change from visit i to visit i+1 of the difference between treated and sham eye in all subjects attending visit i and i + 1. The sensitivity analysis will be a one sample t-test performed on the difference between treated and sham eyes at Week 48. This method assumes that the evolution of drop-out is similar in terms of between eye differences to that of subjects who were followed-up.

The third imputation method will apply the same Rule 1 but for Rule 2 the last available data will be carried forward for the sham eye and the worst available value (either sham or treated eye) will be carried forward for the treated eye. This should be the most conservative imputation method.

13 ETHICS AND RESPONSIBILITIES

13.1 Good Clinical Practice

The current study will comply with the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements.

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH GCP guidelines, and applicable regulatory and country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides the public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki and that the clinical study data are credible.

13.2 Data and Safety Monitoring Board

An independent DSMB will be constituted and responsible for periodically reviewing study data to assure the continued safe conduct of the study. The DSMB will meet to review the data at least every 6 months. Operational and logistical details will be provided in a separate DSMB charter.

13.3 Institutional Review Board/Independent Ethics Committee

The local IRB/IEC to whom an Investigator is responsible has primary responsibility over any clinical trial performed at that location. The protocol will be reviewed by an independent and appropriately constituted IRB/IEC. Study enrolment and protocol-related procedures, which do not form part of the subject's normal clinical treatment, will not be performed until the IRB/IEC of record has provided written approval of the protocol or a modification thereof. The IRB/IEC must be constituted and operate in accordance with the principles and requirements of ICH GCP.

Study drug can only be supplied to the Investigator after documentation of all ethical and legal requirements for starting the study have been received by the Sponsor. This documentation must also include an IRB/IEC membership list that contains members' occupations. If the IRB/IEC will not disclose the names of the committee members, the IRB/IEC Federal-wide Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/IEC should mention the study title, study code, study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

13.4 Informed Consent

Prior to the subject incurring the first study-related procedure, the Investigator or designated individual will explain to each subject and parent/legal guardian (if applicable),

the nature of the study, its purpose, procedures, expected duration, alternative therapies available, and the benefits and risks involved in study participation. All informed consent documents, pediatric assent documents, and other documents used in the conduct of the study will have been approved by an IRB/IEC. For adults who are unable to consent for themselves (e.g., subject has a mental incapacity) consent can be obtained from the subject's legal representative prior to the recruitment of that subject into the trial. If the subject is unable to understand the ICF or assent form due to language barrier and the ICF and assent form are not available in the subject's language, the subject should not be enrolled in the study. Subjects and parents/legal guardians (if applicable) will be given consent documents and pediatric subjects will be given assent documents to review and will have the opportunity to ask questions. Subjects and parents/legal guardians (if applicable) will be informed of the subject's right to withdraw from the study at any time without prejudice. The potential subject and parent/legal guardian (if applicable) should be able to answer simple questions about the study after the ICF and assent form (as applicable) have been reviewed and explained.

After this explanation and before any study-specific procedures have been performed, the subject or parent/legal guardian (if applicable) will voluntarily sign and date the ICF to indicate desire to participate in the study or their informed consent for the pediatric subject's participation. Subjects under the legal age of consent will voluntarily sign the pediatric assent form to indicate desire to participate in the study. The Investigator will also sign and date the ICF and assent form. The time (hour and minute) the consent is signed must also be recorded by the subject or parent/legal guardian (on the ICF), the pediatric subject (if applicable on the pediatric assent form), and the person obtaining consent (on both forms as applicable).

If the subject is of the legal age of consent but is unable to read the informed consent document, presence of an impartial witness is required to confirm the contents of the document were explained to the subject. The impartial witness must sign the ICF. The subject must always be asked to sign or mark the form regardless of their vision.

Prior to participation in the study, the subject (if of the legal age of consent) or parent/legal guardian (if the subject is under the legal age of consent) will receive copies of the signed and dated ICF and signed and dated assent form (if applicable) along with an emergency card with contact information for the Investigator and site staff in the event of a medical emergency during the study.

13.5 Case Report Forms and Study Records Management

The Investigator is responsible for the quality of the data recorded in the CRFs. The data recorded should be a complete and accurate account of the subject's record collected during the study. Study data are not to be gathered directly onto the CRF but must be gathered onto primary source documents at the clinical site. Completion of source documents will precede the completion of the CRF. 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. Source documents will include, but are not limited

to, progress notes, electronic data, screening logs, 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 CRF 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 CRFs and source documents for every subject that signed an informed consent. Site staff will be trained on the CRF completion guidelines and requirements for source documentation.

Completed CRFs will be reviewed by the study monitor in line with CRF review guidelines for the study to ensure completeness and consistency. The Sponsor or its designee will review every subject's CRF with source data verification for at least all critical data points. The source data verification plan for this study will define the level of source data verification required for non-critical data points. Screen failure CRF and source documents require only source data verification for critical data points such as informed consent, AEs, reason for termination, and inclusion/exclusion. Any discrepancies found during the CRF review will be clarified by the Investigator or designated individual. This includes CRF reviews at the site by the Sponsor or its designee, or during quality assurance review of the data.

An explanation must be documented for any missing data. Any changes to information in the study progress notes and other source documents will be initialed and dated on the day the change is made 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 in the source documentation by the clinician.

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

13.6 Access to Source Documentation

The Investigator must agree to complete a subject identification and enrolment log to permit 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 will be treated as confidential and will be filed by the Investigator 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 initials and assigned

number only. The Investigator must also complete a subject-screening 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 for the following to confirm data collected in the CRF: 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; study drug administered; date of study completion or early discontinuation, and reason for early discontinuation if applicable.

13.7 Study Files and Record Retention

All documents pertaining to the study, including all versions of the approved study protocol, copy of the informed consent document and Health Insurance Portability and Accountability Act documents, completed CRFs, source documents (subject records, hospital records, laboratory records, drug accountability records, etc.), 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.

13.8 Data Generation and Analysis

13.8.1 Data Collection and Data Management

Study specific data that has been outlined in the protocol will be entered into the clinical database by individual(s) designated by the Investigator. Data is verified electronically using a series of on-line programmed edit checks that have been 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 CRA and site staff. CRAs will review and verify all data collected in the CRF against source documentation during scheduled monitoring visits. The CRA will work closely with the site staff to address any discrepancies which have been found so that proper resolutions can be made and documented in the clinical database. An audit trail within the system will track all changes made to the data.

13.8.2 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.

13.9 Financial Disclosure

The disclosure of any financial interests from each Investigator or sub-Investigator, 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 is required for this study. The collection of this financial interest information at the start of the study, and at the completion of the study and 1 year following study completion, is required by the FDA when submitting a marketing application and is in line with the GCP requirement to consider any potential conflicts of interest.

14 AUDITING AND MONITORING

In accordance with applicable regulations, GCP, and Sponsor procedures, the clinical monitor(s) will periodically contact the site, including conducting on-site visits at intervals agreed upon by the Investigator and documented in the Clinical Monitoring Plan and the Site Initiation Visit Report.

The clinical monitor(s) will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel. In accordance with applicable regulations and GCP guidelines, the Investigator shall make available for direct access all study-related records upon request of the Sponsor, the Sponsor's agents, clinical monitor(s), auditors, and/or IRB/IEC. The Sponsor's monitors will visit the site during the study in addition to maintaining frequent telephone and written communication. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

The Investigator must allow the clinical monitor(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the clinical monitor(s) to discuss findings and any relevant issues.

15 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor or their designee. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. The Sponsor or their designee will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/IEC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

16 STUDY REPORT AND PUBLICATIONS

A clinical study report will be prepared following completion of the study. The report will be a record of the total study conduct and will be subject to Sponsor approval and restrictions on distribution/disclosure.

The study data will be owned by the Sponsor. Publication of any and all data will be at the discretion of the Sponsor. The Investigator will not disseminate, present, or publish any of the study data without the prior written approval of the Sponsor to do so.

17 STUDY DISCONTINUATION

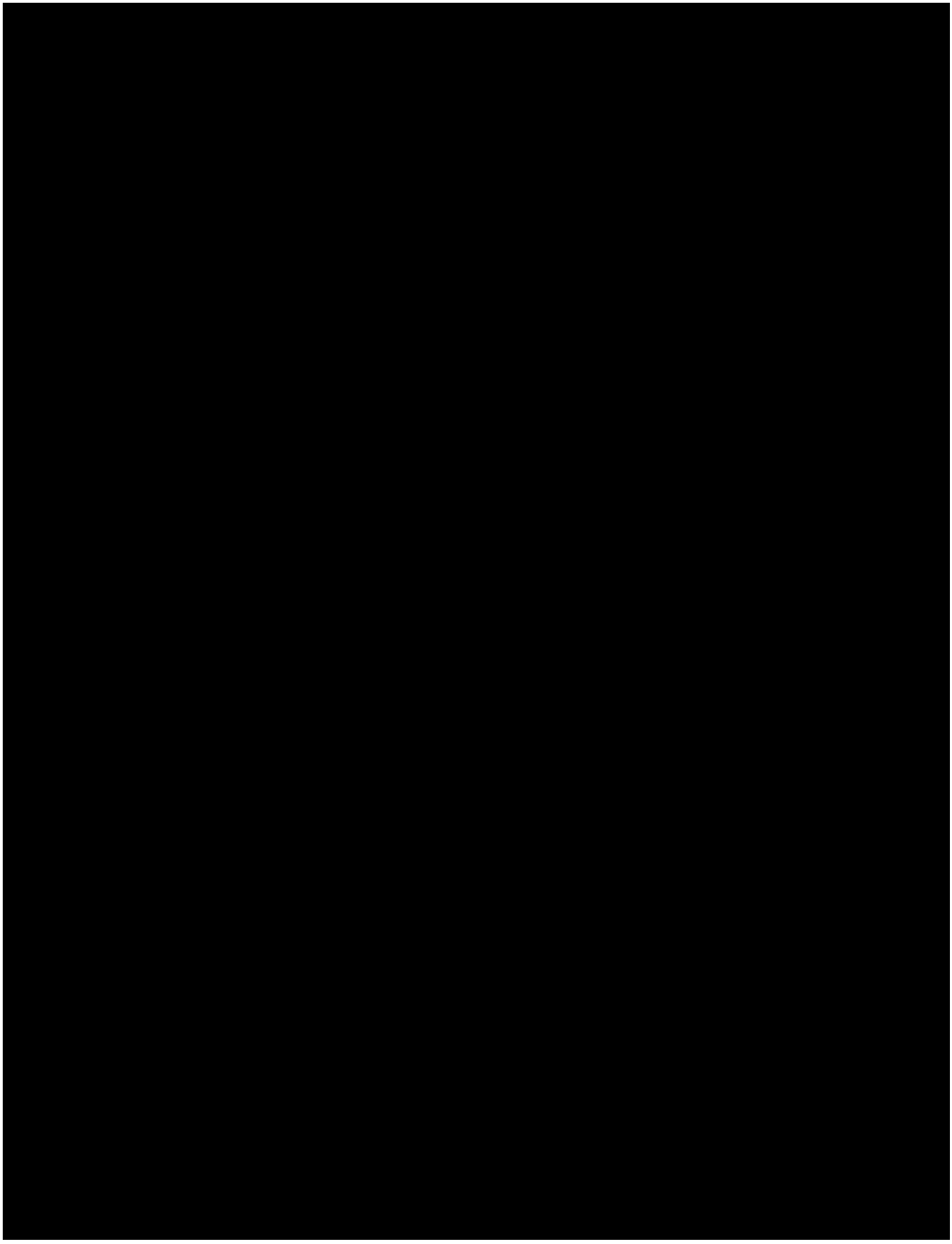
Upon completion of the study, study closeout activities must be conducted by the Sponsor or their designee in conjunction with the Investigator, as appropriate.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reason[s] for taking such action) at that time. The Sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension or termination. If the study is prematurely discontinued, all study data and study drug remaining on site must be returned to the Sponsor or its designee.

18 CONFIDENTIALITY

All subject-identifying documentation generated in this study must be considered confidential and must not be disclosed to any persons not directly concerned with the study without written permission from the subject. However, authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. 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 Sponsor.

Each subject will be identified by initials and an assigned subject number when reporting study information to any entity outside of the study center. Data containing subject identification will not be removed from the study center without subject identifiers having been redacted.



20.2 APPENDIX II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly

Helsinki, Finland, June 1964

And amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

And the:

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for

review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

20.5 APPENDIX V – Masking of the Treated Eye and Performance of the Primary Analysis

The following measures will be applied to keep the integrity of the database:

- The first masked review of data will be performed as late as possible, once all SAS programs are validated for study GS-LHON-CLIN-03A.
- Data will be cleaned and frozen up to and including the Week 48 visit.
- The cut-off date for the cleaning of subject visits will be recorded.
- A snapshot of the cleaned data base will be kept for statistical purposes and for possible inspection. The date of the snapshot will be recorded.
- A procedure will be written to trace data modification after the freeze of the database. Modifications will be listed in an appendix.
- The listing per subject of frozen visits (at least up to Week 48) will be provided and the status "ongoing" will be provided for unfrozen visits.
- A table will indicate the number of subjects with frozen data at each visit (for example 36/36 subjects at Week 48, 28/36 subjects at Week 72 and 23/36 subjects at Week 96).
- The masked team in charge of the collection and verification of data will remain masked up until the last visit (Week 96) of the last subject.
- For International coordinating investigators who review the Week 48 study report all efforts will be made to maintain their making regarding the individual subject results.
- Statistical results will be disclosed as late as possible. Date of disclosure will be recorded and a second snapshot of the data base will be done at that time.
- Review of listings of individual data will be restricted to very few people (e.g. for pharmacovigilance for safety data).
- The final masked review (Week 96) will exclude people who had access to unmasked individual subject data.
- No amendment of the SAP will be possible after the break of the randomization code. Any addition will be considered *a posteriori*/*ad-hoc* analyses.