Clinical trial results:
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

Summary

EudraCT number	2015-001265-11
Trial protocol	DE GB IT
Global end of trial date	04 July 2019

Results information

Result version number	v1 (current)
This version publication date	02 February 2020
First version publication date	02 February 2020

Trial information

Trial identification

Sponsor protocol code	GS-LHON-CLIN-03A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02652767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GenSight Biologics
Sponsor organisation address	74 Rue du Faubourg Saint-Antoine, Paris, France, 75012
Public contact	Regulatory Affairs Director, GENSIGHT-BIOLOGICS, 0033 176217220, ipengue@gensight-biologics.com
Scientific contact	Regulatory Affairs Director, GENSIGHT-BIOLOGICS, 0033 176217220, ipengue@gensight-biologics.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 August 2018
Global end of trial reached?	Yes
Global end of trial date	04 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 participants affected for 6 months or less by Leber hereditary optical neuropathy (LHON).

Protection of trial subjects:

In order to ensure the protection of trial participants, a Data and Safety Monitoring Board meeting was convened at least every 6 months to review the safety data.
Additionally, to minimize pain, an intraocular pressure (IOP) lowering agent was administered 60-120 minutes prior to investigational medicinal product (IMP) administration.
Finally, the following safety assessments were conducted:
- IOP of each eye was measured using Goldmann applanation tonometry according to the usual procedure at each site.
- A fluorescein angiogram was obtained at post-IMP administration visits at which the investigator documents the initial presence of significant vitreous inflammation that requires treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	39
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	4
Adults (18-64 years)	34
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 39 participants were enrolled across 7 sites in 4 European countries and the United States.

Pre-assignment

Screening details:

A total of 39 participants were enrolled. The right eye of each participant was randomly assigned either GS010 or the sham procedure in a 1:1 ratio. The left eye of each participant recieved the other treatment, which was not allocated to the right eye.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Arm title	Overall trial: All participants

Arm description:

All participants who were enrolled and received both study treatments, GS010 and sham. All participants received both GS010 and the sham procedure simultaneously. The right eye of each participant was randomly assigned to receive either GS010 or the sham treatment. The left eye received the treatment which was not allocated to the right eye.

GS010: Either the right or left eye received one single dose of GS010 (9E10 vg/eye) via an intravitreal (IVT) injection. The volume of the injected formula was 90 µL. The injection was performed in the vitreous humor under local anesthesia.

Sham procedure: One single Sham IVT injection was performed by applying pressure to the eye at the location of a typical IVT injection procedure, using the blunt end of a syringe without a needle.

Arm type	Experimental
Investigational medicinal product name	GS010 (rAAV2/2-ND4)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravitreal use

Dosage and administration details:

9E10 vg/eye (volume of injection of 90 µL) by intravitreal injection.

Investigational medicinal product name	Sham
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Route of administration not applicable

Dosage and administration details:

Sham procedure was performed by applying pressure to the eye at the location of a typical procedure using the blunt end of a syringe without a needle.

Number of subjects in period 1	Overall trial: All participants
Started	39
Participants who completed Week 48	38
Completed	35
Not completed	4
Adverse event, serious fatal	2
Consent withdrawn by subject	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	4	4	
Adults (18-64 years)	34	34	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	36.3		
standard deviation	± 15.5	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	32	32	
Weight Units: kg			
arithmetic mean	73.9		
standard deviation	± 17.8	-	
Height Units: cm			
arithmetic mean	174.5		
standard deviation	± 7.7	-	

End points

End points reporting groups

Reporting group title	Overall trial: All participants

Reporting group description:

All participants who were enrolled and received both study treatments, GS010 and sham. All participants received both GS010 and the sham procedure simultaneously. The right eye of each participant was randomly assigned to receive either GS010 or the sham treatment. The left eye received the treatment which was not allocated to the right eye.

GS010: Either the right or left eye received one single dose of GS010 (9E10 vg/eye) via an intravitreal (IVT) injection. The volume of the injected formula was 90 µL. The injection was performed in the vitreous humor under local anesthesia.

Sham procedure: One single Sham IVT injection was performed by applying pressure to the eye at the location of a typical IVT injection procedure, using the blunt end of a syringe without a needle.

Subject analysis set title	GS010 treatment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants and eyes that were treated with GS010 in either the right or left eye. The same participants also received sham comparator in the eye (right or left) that did not receive GS010 IVT injection. One participant was excluded from the intent-to-treat population due to receiving a smaller volume of study treatment than specified in the protocol.

Subject analysis set title	Sham comparator
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants and eyes that were given the sham comparator in either the right or left eye. The same participants also received GS010 IVT injection in the eye (right or left) that did not receive sham comparator. One participant was excluded from the intent-to-treat population due to receiving a smaller volume of study treatment than specified in the protocol.

Primary: Change From Baseline in ETDRS Visual Acuity (Quantitative Score) at Week 48

End point title	Change From Baseline in ETDRS Visual Acuity (Quantitative Score) at Week 48

End point description:

Visual acuity was derived from the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Visual acuity is measured in "logarithm of the minimal angle of resolution" (LogMAR), which was derived from the number of letters participants could read on the ETDRS chart.
1 ETDRS line = 5 letters
1 ETDRS line = 0.1 LogMAR
A lower LogMAR score denotes better visual acuity. A positive change from baseline indicates a worsening in symptoms.
Change = (Week 48 score - Baseline score).

End point type	Primary

End point timeframe:

Baseline and Week 48

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[1]	38[2]		
Units: LogMAR				
least squares mean (standard error)	0.380 (± 0.129)	0.392 (± 0.129)		

Notes:

[1] - Intent-to-treat (ITT) population.

[2] - Intent-to-treat (ITT) population.

Statistical analyses

Statistical analysis title	Difference between GS010 Eyes and Sham Eyes

Statistical analysis description:

The analysis compared GS010 treated eyes to Sham eyes of all 38 intent-to-treat participants.

Comparison groups	GS010 treatment v Sham comparator
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.889
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.182
upper limit	0.158

Secondary: Change From Baseline in ETDRS Visual Acuity (Quantitative Score)

End point title	Change From Baseline in ETDRS Visual Acuity (Quantitative Score)

End point description:

Visual acuity was derived from the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Visual acuity is measured in "logarithm of the minimal angle of resolution" (LogMAR), which was derived from the number of letters participants could read on the ETDRS chart.
1 ETDRS line = 5 letters
1 ETDRS line = 0.1 LogMAR
A lower LogMAR score denotes better visual acuity. A positive change from baseline indicates a worsening in symptoms.
Change = (Week 72 score - Baseline score) or (Week 96 score - Baseline score).
Missing data were imputed by the linear interpolation method.

End point type	Secondary

End point timeframe:

Baseline; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[3]	38[4]		
Units: LogMAR				
least squares mean (standard error)				
Week 72	0.192 (± 0.104)	0.216 (± 0.104)		
Week 96	0.178 (± 0.120)	0.207 (± 0.120)		

Notes:

[3] - Intent-to-treat (ITT) population.

[4] - Intent-to-treat (ITT) population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Eye Responders to Treatment

End point title	Number of Eye Responders to Treatment

End point description:

An eye was determined as a responder to treatment based on 2 different definitions.

Definition 1: An eye responder was defined by an improvement of the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score of at least 15 letters compared to Baseline, or a final visual acuity greater than a Snellen acuity equivalent of 20/200.
Definition 2: An eye responder was defined by an improvement of the ETDRS score of at least 20 letters compared to Baseline.

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[5]	38[6]		
Units: Number of Eyes				
Week 48 Definition 1	4	3		
Week 48 Definition 2	9	10		
Week 72 Definition 1	6	5		
Week 72 Definition 2	11	9		
Week 96 Definition 1	7	5		
Week 96 Definition 2	13	11		

Notes:

[5] - Intent-to-treat (ITT) population.

[6] - Intent-to-treat (ITT) population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subject Responders to Treatment

End point title	Number of Subject Responders to Treatment

End point description:

A subject responder was defined as a participant whose Early Treatment Diabetic Retinopathy Study (ETDRS) score of the treated eye (that received GS010), was at least 15 letters better than the sham eye, or whose treated eye had a "logarithm of the minimal angle of resolution" (LogMAR) acuity score of at least 0.3 LogMAR better than the sham eye.

End point type	Secondary

End point timeframe:

Week 48; Week 72 and Week 96

End point values	Overall trial: All participants			
Subject group type	Reporting group			
Number of subjects analysed	38[7]			
Units: Number of Participants				
Week 48	4			
Week 72	2			
Week 96	5			

Notes:

[7] - Intent-to-treat (ITT) population. Full sample size analysis population was used at Week 96.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in GCL Macular Volume

End point title	Change From Baseline in GCL Macular Volume

End point description:

Ganglion cell layer (GCL) macular volume was measured as a parameter of spectral domain-optical coherence tomography (SD-OCT). SD-OCT was obtained with the Spectralis® OCT (Heidelberg Engineering).

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[8]	37[9]		
Units: mm^3				
least squares mean (standard error)				
Week 48	-0.184 (± 0.014)	-0.207 (± 0.014)		
Week 72	-0.204 (± 0.015)	-0.226 (± 0.015)		
Week 96	-0.208 (± 0.015)	-0.221 (± 0.015)		

Notes:

[8] - ITT population. Week 48 N 36
Week 72 N 33
Week 96 N 33
Data at Baseline and the post-dose visit.
[9] - ITT population. Week 48 N 37
Week 72 N 34
Week 96 N 33
Data at Baseline and the post-dose visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RNFL Temporal Quadrant Thickness

End point title	Change From Baseline in RNFL Temporal Quadrant Thickness

End point description:

Retinal nerve fiber layer (RNFL) temporal quadrant thickness was measured as a parameter of spectral domain-optical coherence tomography (SD-OCT). SD-OCT was obtained with the Spectralis® OCT (Heidelberg Engineering).

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37[10]	37[11]		
Units: µm				
least squares mean (standard error)				
Week 48	-22.8 (± 1.0)	-24.7 (± 1.0)		
Week 72	-25.5 (± 0.9)	-26.0 (± 0.9)		
Week 96	-24.2 (± 0.8)	-26.1 (± 0.8)		

Notes:

[10] - ITT population. Week 48 N 37
Week 72 N 34
Week 96 N 32
Data at Baseline and the post-dose visit.
[11] - ITT population. Week 48 N 37
Week 72 N 34
Week 96 N 33
Data at Baseline and the post-dose visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in RNFL Papillomacular Bundle Thickness

End point title	Change From Baseline in RNFL Papillomacular Bundle Thickness

End point description:

Papillomacular bundle thickness was measured as a parameter of spectral domain-optical coherence tomography (SD-OCT). SD-OCT was obtained with the Spectralis® OCT (Heidelberg Engineering).

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37[12]	37[13]		
Units: µm				
least squares mean (standard error)				
Week 48	-10.4 (± 1.0)	-12.4 (± 1.0)		
Week 72	-12.8 (± 1.0)	-13.1 (± 1.0)		
Week 96	-11.2 (± 1.0)	-13.3 (± 1.0)		

Notes:

[12] - ITT population. Week 48 N 37
Week 72 N 34
Week 96 N 32
Data at Baseline and the post-dose visit.

[13] - ITT population. Week 48 N 37
Week 72 N 34
Week 96 N 33
Data at Baseline and the post-dose visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ETDRS Total Macular Volume

End point title	Change From Baseline in ETDRS Total Macular Volume

End point description:

Early Treatment Diabetic Retinopathy Study (ETDRS) total macular volume was measured as a parameter of spectral domain-optical coherence tomography (SD-OCT). SD-OCT was obtained with the Spectralis® OCT (Heidelberg Engineering).

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[14]	37[15]		
Units: mm^3				
least squares mean (standard error)				
Week 48	-0.578 (± 0.041)	-0.708 (± 0.040)		
Week 72	-0.686 (± 0.048)	-0.782 (± 0.048)		
Week 96	-0.720 (± 0.050)	-0.800 (± 0.050)		

Notes:

[14] - ITT population. Week 48 N 36
Week 72 N 33
Week 96 N 33
Data at Baseline and the post-dose visit.
[15] - ITT population. Week 48 N 37
Week 72 N 34
Week 96 N 33
Data at Baseline and the post-dose visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Foveal Threshold Sensitivities Obtained With HVF Analyzer II

End point title	Change From Baseline in the Foveal Threshold Sensitivities Obtained With HVF Analyzer II

End point description:

The assessment of standardized automated visual fields was measured using the Humphrey Visual Field (HVF) Analyzer II. Automated visual fields included the assessment of foveal threshold sensitivities. Foveal threshold sensitivity is measured in decibels (dB), which ranges from 0 dB to 50 dB. A sensitivity threshold of 0 dB indicates not being able to see the most intense perimetric stimulus, while higher dB indicates better/normal foveal vision. A positive change from baseline indicates an improvement of symptoms.

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11[16]	8[17]		
Units: decibels (dB)				
arithmetic mean (standard deviation)				
Week 48	3.5 (± 12.3)	-7.4 (± 12.8)		
Week 72	6.3 (± 7.8)	-5.1 (± 11.9)		
Week 96	3.3 (± 12.7)	1.4 (± 19.5)		

Notes:

[16] - ITT population. Week 48 N 11
Week 72 N 7
Week 96 N 6
Data at Baseline and the post-dose visit.
[17] - ITT population. Week 48 N 7
Week 72 N 7
Week 96 N 8
Data at Baseline and the post-dose visit.

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Field Mean Deviation in Decibels of Sensitivity Obtained With HVF Analyzer II

End point title	Visual Field Mean Deviation in Decibels of Sensitivity Obtained With HVF Analyzer II

End point description:

The assessment of standardized automated visual fields was measured using the Humphrey Visual Field (HVF) Analyzer II. Automated visual fields included the assessment of the mean deviation (MD) in decibels (dB) of sensitivity.

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[18]	38[19]		
Units: decibels (dB)				
arithmetic mean (standard deviation)				
Baseline MD	-16.26 (± 10.59)	-16.73 (± 11.48)		
Week 48 MD	-24.26 (± 9.37)	-23.76 (± 10.40)		
Week 72 MD	-23.33 (± 9.41)	-22.94 (± 10.11)		
Week 96 MD	-23.31 (± 9.41)	-22.70 (± 9.88)		

Notes:

[18] - ITT set
Baseline N 38
Week 48 N 37
Week 72 & Week 96 N 34
Data at Baseline and post-dose visit
[19] - ITT set
Baseline N 38
Week 48 N 37
Week 72 & Week 96 N 33
Data at Baseline and post-dose visit

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Contrast Sensitivity

End point title	Change From Baseline in Contrast Sensitivity

End point description:

The assessment of contrast sensitivity was measured using the Pelli-Robson chart. The chart uses letters arranged in groups whose contrast varies from high to low. Participants read the letters, starting with the highest contrast, until they are unable to read 2 or 3 letters in a single group. Each eye is assigned a score based on the contrast of the last group in which 2 or 3 letters were correctly read, ranging from 0 to 2.2 "log of contrast sensitivity" (LogCS) units. A score of 2.0 LogCS, represents a normal sensitivity contrast, and indicates the eye was able to detect 2 of the 3 letters with a contrast of 1 percent (contrast sensitivity = 100 percent or log 2). Scores less than 2.0 signify poorer contrast sensitivity. Pelli-Robson contrast sensitivity score of less than 1.5 is consistent with visual impairment and a score of less than 1.0 represents in visual disability. A negative change from baseline indicates worsening in symptoms.

End point type	Secondary

End point timeframe:

Baseline; Week 48; Week 72 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[20]	38[21]		
Units: LogCS				
least squares mean (standard error)				
Week 48	-0.35 (± 0.07)	-0.33 (± 0.07)		
Week 72	-0.25 (± 0.07)	-0.28 (± 0.07)		
Week 96	-0.27 (± 0.07)	-0.25 (± 0.07)		

Notes:

[20] - Intent-to-treat (ITT) population.

[21] - Intent-to-treat (ITT) population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Color Vision

End point title	Change From Baseline in Color Vision

End point description:

The assessment of color vision was measured using the Farnsworth-Munsell 100-Hue Color Test. Each of the 4 trays consisted of 21 caps. Participants were asked to sort the randomly arranged caps following the hue order from the first to the last fixed caps. The total error score (TES) was derived by the frequency the caps were misplaced and the severity, or distance of the misplacement.

Errors were made whenever caps were misplaced from the correct order. Error scores were calculated according to the distance between any two caps. The error score for each individual cap was the sum of the difference between the number of that cap and the numbers of the cap adjacent to it, minus 2. TES was the total sum of the error scores of the entire set of caps.

The best possible score was 0 and there is no defined upper limit to the total error score range. A lower score indicates improved color discrimination ability. A negative change from baseline indicates an improvement in symptoms.

End point type	Secondary

End point timeframe:

Baseline; Week 48 and Week 96

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21[22]	21[23]		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 48	133.1 (± 290.7)	235.6 (± 392.3)		
Week 96	97.7 (± 342.2)	213.5 (± 393.1)		

Notes:

[22] - ITT population.
Week 48 N 18
Week 96 N 21
Data at Baseline and post-dose visit.

[23] - ITT population.
Week 48 N 20
Week 96 N 21
Data at Baseline and post-dose visit.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose to the end of study (a maximum of 96 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Overall trial: All participants

Reporting group description:

All participants who were enrolled and received both study treatments, GS010 and sham. All participants received both GS010 and the sham procedure. The right eye of each participant was randomly assigned to receive either GS010 or the sham treatment. The left eye received the treatment which was not allocated to the right eye.

GS010: One single intravitreal (IVT) injection containing 9E10 viral genomes in 90 µl balanced salt solution (BSS) plus 0.001% Pluronic F68®. The IVT injection was performed in the vitreous humor under local anaesthesia.

Sham procedure: The sham IVT injection was performed by applying pressure to the eye at the location of a typical IVT injection procedure, using the blunt end of a syringe without a needle.

Serious adverse events	Overall trial: All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 39 (7.69%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Alcoholic liver disease			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Alcohol withdrawal syndrome			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Overall trial: All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 39 (97.44%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Blood glucose increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Neutrophil count increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
White blood cell count increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

Intraocular pressure increased	Additional description: 1/13 affected participants experienced this event in the sham-treated eyes.		
subjects affected / exposed	13 / 39 (33.33%)		
occurrences (all)	14		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	30		
Migraine			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	10		
Social circumstances			
Alcohol use			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Eye disorders			
Anterior chamber cell			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Anterior chamber flare			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	6		
Anterior chamber inflammation			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	5		
Autoimmune uveitis	Additional description: The verbatim term for all events of "autoimmune uveitis" is "intermediate uveitis".		
subjects affected / exposed	15 / 39 (38.46%)		
occurrences (all)	19		
Chalazion			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Conjunctival haemorrhage	Additional description: 1/7 affected participants experienced this event in the sham-treated eyes.		

subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	13		
Conjunctival hyperaemia	Additional description: 4/5 affected participants experienced this event in the sham-treated eyes.		
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	10		
Corneal disorder			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Eye irritation	Additional description: 1/2 affected participants experienced this event in the sham-treated eyes.		
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Eye pain	Additional description: 1/3 affected participants experienced this event in sham-treated eyes.		
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	8		
Foreign body sensation in eyes	Additional description: 1/2 affected participants experienced this event in sham-treated eyes.		
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Iridocyclitis	Additional description: 2/18 affected participants experienced this event in the sham-treated eyes.		
subjects affected / exposed	18 / 39 (46.15%)		
occurrences (all)	24		
Iris atrophy			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Iris transillumination defect			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Keratic precipitates			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	11		
Macular oedema			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Photopsia			

subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Punctate keratitis	Additional description: 3/18 affected participants experienced this event in sham-treated eyes.		
subjects affected / exposed	18 / 39 (46.15%)		
occurrences (all)	20		
Vitreal cells			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Vitreous disorder			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Vitreous floaters			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Vitritis			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	8		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	7		
Ear infection			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2015	The protocol was revised to incorporate the following: 1. Added the newly-determined names of the current studies (RESCUE and REVERSE) to the protocol. 2. Updated the clinical and nonclinical safety profile of GS010. 3. The objectives, endpoints, and statistical analyses were revised to harmonize with Protocol GS-LHON-CLIN-03B. i. The primary endpoint (both studies) was to be the ETDRS score at 48 weeks compared to Baseline. ii. Secondary acuity endpoints in both studies were to include ETDRS at 96 weeks compared to Baseline, binary response to treatment at 48 and 96 weeks, and the comparison of the strategy of treating better versus worse seeing eyes. 4. Randomization was revised from the better-seeing eye to the right eye of each participant randomized with the left receiving the alternative. 5. Revised the randomization and unmasking methods from envelopes to an interactive voice recognition system. 6. Respiratory rate was removed from the measured vital signs. 7. Applanation tonometry was further specified as Goldmann applanation tonometry. 8. The color vision test was changed from the 15 Hue color test to the Farnsworth Munsell 100 Hue Color Test. 9. Added a section for Study Duration with a definition of End of Study as last subject’s last visit. 10. The data collected by the SD-OCT assessment were simplified. 11. More specific time frames were assigned to some secondary endpoints. 12. Added color fundus photos at Visit 1 for Baseline and Visits 4 to12 as necessary if the participant had vitreous inflammation. 13. Added all vision-related testing to Visit 1. 14. Specific instructions were added on establishing and maintaining the study masking and procedures for unmasking. 15. The timing of the primary analysis was revised so that the primary efficacy analysis can be performed after all participants complete Week 48. 16. Changed the term “patients” to “subjects” when referring to study participants.
22 February 2016	The protocol was revised to incorporate the following: 1. Added the ClinicalTrials.gov identifier for the trial. 2. Made refraction for BCVA required at each study follow-up visit regardless of change in visual acuity. 3. Required ND4 genotyping to be performed for all participants in an appropriately certified central study laboratory. 4. Clarified in the Schedule of Events that QoL questionnaires should be administered before visual acuity tests were conducted. 5. Clarified the non-selection criteria with regard to participants with well-controlled glaucoma. 6. Updated the appropriate post-reconstitution storage conditions for the investigational product. 7. Clarified the appropriate site personnel who could randomize participants. 8. Widened eligible participant age range to include pediatric participants aged 15 to 18 years and made corresponding changes to the informed consent process to include pediatric participants.

07 November 2016	The protocol was revised to incorporate the following: 1. Updated the job title of one of the study Sponsor contacts. 2. Added the performance of FAs to the protocol when the Investigator documented the initial presence of significant vitreous inflammation that also required treatment per the recommendation of the study DSMB. The FAs served to further characterize the observed vitreous inflammation and potentially guide management/treatment of the vitreous inflammation. 3. Clarified how the duration of vision loss should be calculated for the purpose of determining study eligibility. 4. Clarified which study visits should be conducted by the unmasked study team and how AEs should be followed up by the unmasked study team.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported