



## 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 more than 6 Months and to 12 months by Leber Hereditary Optic Neuropathy Due to the G11778A Mutation in the Mitochondrial NADH Dehydrogenase 4 Gene

#### Summary

EudraCT number	2015-001266-26
Trial protocol	DE GB IT
Global end of trial date	19 December 2018

#### Results information

Result version number	v1
This version publication date	27 December 2019
First version publication date	27 December 2019

#### Trial information

##### Trial identification

Sponsor protocol code	GS-LHON-CLIN-03B
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02652780
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, GEN SIGHT-BIOLOGICS, 0033 176217233, ipengue@gensight-biologics.com
Scientific contact	Regulatory Affairs Director, GEN SIGHT-BIOLOGICS, 0033 176217233, 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	07 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2018
Global end of trial reached?	Yes
Global end of trial date	19 December 2018
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 logarithm of the minimal angle of resolution (LogMAR) in participants affected for more than 6 months and up to 12 months by Leber hereditary optic 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	22 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 States: 20
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 4
Worldwide total number of subjects	37
EEA total number of subjects	17

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)	32
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 37 participants were enrolled across 7 sites in 4 European countries and the United States. The right eye of each participant was randomly allocated either GS010 or Sham in a 1:1 ratio. The left eye of each participant received the other treatment not allocated to the right eye at the same visit.

### Pre-assignment

Screening details:

A total of 49 participants were screened, with 12 resulting in screen failures. 37 participants were randomized and received study treatment.

### 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

Blinding implementation details:

An unmasked team at the site performed all procedures on Day 0 (treatment day) and Day 1 and focused follow-up of ocular AEs commencing on Day 0 and 1 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 on Day 1. The Principal Investigator remained masked until study end.

### Arms

Arm title	Overall trial: All participants
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Arm description:

All participants who were enrolled and received both study treatments, GS010 and Sham. Participants were randomly assigned to receive GS010 in either the right or left eye. The same participants also received the sham comparator in the eye not assigned to GS010 at the same visit.

GS010: Either the right or left eye received one single dose of GS010 via an intravitreal (IVT) injection containing 9E10 viral genomes in 90 µl balanced salt solution (BSS) plus 0.001% Pluronic F68®.

Sham procedure: Either the right or left eye (the eye not randomly assigned to GS010) received the 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:

Dosage: 9E10 vg/eye (volume of injection of 90µL) 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:

The 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.

<b>Number of subjects in period 1</b>	Overall trial: All participants
Started	37
Completed	37

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description:	
All participants who were enrolled and randomized, and who received both treatments, GS010 and Sham.	

Reporting group values	Overall trial	Total	
Number of subjects	37	37	
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)	32	32	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	34.2		
standard deviation	± 15.2	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	29	29	
Weight			
Units: kg			
arithmetic mean	80.1		
standard deviation	± 21.0	-	
Height			
Units: cm			
arithmetic mean	174.4		
standard deviation	± 7.8	-	

## 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. Participants were randomly assigned to receive GS010 in either the right or left eye. The same participants also received the sham comparator in the eye not assigned to GS010 at the same visit.	
GS010: Either the right or left eye received one single dose of GS010 via an intravitreal (IVT) injection containing 9E10 viral genomes in 90 µl balanced salt solution (BSS) plus 0.001% Pluronic F68®.	
Sham procedure: Either the right or left eye (the eye not randomly assigned to GS010) received the 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 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.	
Subject analysis set title	Sham comparator
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All 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.	

### 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:	
Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity LogMAR score 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 0.1 LogMAR = 5 ETDRS letters 15 ETDRS letters = 0.3 LogMAR A negative change from baseline indicates an improvement in visual acuity.	
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	37	37		
Units: LogMAR				
least squares mean (standard error)	-0.219 (± 0.055)	-0.211 (± 0.055)		

## Statistical analyses

<b>Statistical analysis title</b>	Difference between GS010 Eyes and Sham Eyes
Statistical analysis description: The analysis compared GS010 treated eyes to Sham eyes of all 37 intent-to-treat participants.	
Comparison groups	GS010 treatment v Sham comparator
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.8783 <sup>[2]</sup>
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.102

Notes:

[1] - A mixed model of analysis of covariance (ANCOVA) was used with change from baseline at week 48 as the response, and participants, eyes of the participant as random factor, treatment and baseline LogMAR value as covariates in the model.

[2] - P-value is used to assess the significance of the difference between All-GS010 and All-Sham with respect to change of LogMAR from baseline using Wilcoxon Signed-Rank test.

## Secondary: Change from Baseline in ETDRS Visual Acuity (Quantitative Score) at Week 96

End point title	Change from Baseline in ETDRS Visual Acuity (Quantitative Score) at Week 96
End point description: Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity LogMAR score 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 0.1 LogMAR = 5 ETDRS letters 15 ETDRS letters = 0.3 LogMAR A negative change from baseline indicates an improvement in visual acuity.	
End point type	Secondary
End point timeframe: Baseline and Week 96	

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	37		
Units: LogMAR score				
least squares mean (standard deviation)	-0.308 (± 0.068)	-0.259 (± 0.068)		

## Statistical analyses



No statistical analyses for this end point

### Secondary: Number of Eye Responders to Treatment at Week 48 and Week 96

End point title	Number of Eye Responders to Treatment at Week 48 and Week 96
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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 (a score of at least 1 letter).

Definition 2: An eye responder was defined by an ETDRS score of at least 20 letters compared to baseline.

End point type	Secondary
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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	37	37		
Units: Participants				
Week 48 Definition 1	7	5		
Week 48 Definition 2	10	13		
Week 96 Definition 1	12	6		
Week 96 Definition 2	17	19		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subject Responders to Treatment at Week 48 and Week 96

End point title	Number of Subject Responders to Treatment at Week 48 and Week 96
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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, is at least 15 letters better than the sham eye, or whose treated eye has a logarithm of the minimal angle of resolution (LogMAR) acuity of at least 0.3 LogMAR better than the sham eye.

End point type	Secondary
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End point timeframe:

Week 48 and Week 96

<b>End point values</b>	Overall trial: All participants			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Participants				
Week 48	37			
Week 96	37			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in GCL Macular Volume at Week 48 and Week 96

End point title	Change from Baseline in GCL Macular Volume at Week 48 and Week 96
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 and Week 96

<b>End point values</b>	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36 <sup>[3]</sup>	36 <sup>[4]</sup>		
Units: mm <sup>3</sup>				
least squares mean (standard error)				
Week 48	-0.003 (± 0.012)	-0.038 (± 0.012)		
Week 96	-0.018 (± 0.012)	-0.031 (± 0.012)		

Notes:

[3] - Week 48 N = 36

Week 96 N = 36

All participants with data at baseline and Week 48 or Week 96.

[4] - Week 48 N = 36

Week 96 N = 36

All participants with data at baseline and Week 48 or Week 96.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in RNFL Temporal Quadrant Thickness at Week 48 and Week 96

End point title	Change from Baseline in RNFL Temporal Quadrant Thickness at Week 48 and Week 96
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
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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	37 <sup>[5]</sup>	36 <sup>[6]</sup>		
Units: µm				
least squares mean (standard error)				
Week 48	-0.562 (± 0.988)	-3.354 (± 1.017)		
Week 96	-1.791 (± 0.974)	-2.042 (± 0.951)		

Notes:

[5] - Week 48 N = 37

Week 96 N = 35

All participants with data at baseline and Week 48 or Week 96.

[6] - Week 48 N = 35

Week 96 N = 36

All participants with data at baseline and Week 48 or Week 96.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Papillomacular Bundle Thickness at Week 48 and Week 96

End point title	Change from Baseline in Papillomacular Bundle Thickness at Week 48 and Week 96
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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
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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	37 <sup>[7]</sup>	36 <sup>[8]</sup>		
Units: µm				
least squares mean (standard error)				
Week 48	1.6 (± 1.3)	-1.0 (± 1.4)		
Week 96	1.2 (± 1.3)	0.7 (± 1.3)		

Notes:

[7] - Week 48 N = 37

Week 96 N = 35

All participants with data at baseline and Week 48 or Week 96.

[8] - Week 48 N = 35

Week 96 N = 36

All participants with data at baseline and Week 48 or Week 96.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in ETDRS Total Macular Volume at Week 48 and Week 96

End point title	Change from Baseline in ETDRS Total Macular Volume at Week 48 and Week 96
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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
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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	36 <sup>[9]</sup>	36 <sup>[10]</sup>		
Units: mm <sup>3</sup>				
least squares mean (standard error)				
Week 48	-0.104 (± 0.046)	-0.224 (± 0.046)		
Week 96	-0.200 (± 0.037)	-0.265 (± 0.037)		

Notes:

[9] - Week 48 N = 36

Week 96 N = 36

All participants with data at baseline and Week 48 or Week 96.

[10] - Week 48 N = 36

Week 96 N = 36

All participants with data at baseline and Week 48 or Week 96.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Foveal Threshold Sensitivities Obtained With HVF Analyzer II at Week 48 and Week 96

End point title	Change From Baseline in the Foveal Threshold Sensitivities Obtained With HVF Analyzer II at Week 48 and Week 96
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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 and Week 96	

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9 <sup>[11]</sup>	11 <sup>[12]</sup>		
Units: decibel (dB)				
arithmetic mean (standard deviation)				
Week 48: Foveal Threshold Sensitivity	0.7 (± 8.9)	-0.5 (± 11.9)		
Week 96: Foveal Threshold Sensitivity	1.3 (± 8.0)	2.4 (± 10.8)		

Notes:

[11] - Week 48 N = 9

Week 96 N = 8

[12] - Week 48 N = 11

Week 96 N = 9

### Statistical analyses

No statistical analyses for this end point

### Secondary: Visual Field Mean Deviation in Decibels of Sensitivity Obtained With HVF Analyzer II at Week 48 and Week 96

End point title	Visual Field Mean Deviation in Decibels of Sensitivity Obtained With HVF Analyzer II at Week 48 and Week 96
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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 and Week 96	

End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	37		
Units: decibels (dB)				
arithmetic mean (standard deviation)				
Baseline MD	-25.99 (± 8.37)	-24.94 (± 9.70)		
Week 48 MD	-22.83 (± 9.43)	-22.94 (± 9.80)		
Week 96 MD	-23.22 (± 8.98)	-22.43 (± 9.39)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Contrast Sensitivity at Week 48 and Week 96

End point title	Change from Baseline in Contrast Sensitivity at Week 48 and Week 96
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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. A score of 2.0 log of contrast sensitivity (LogCS) units, which represents a normal sensitivity contrast, indicates that 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 positive change from baseline indicates improvement in symptoms.

End point type	Secondary
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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	37	37		
Units: LogCS score				
least squares mean (standard error)				
Week 48	0.19 ( $\pm$ 0.05)	0.09 ( $\pm$ 0.05)		
Week 96	0.22 ( $\pm$ 0.06)	0.12 ( $\pm$ 0.06)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Color Vision at Week 48 and Week 96

End point title	Change from Baseline in Color Vision at Week 48 and Week 96
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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 movable 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 was derived by counting the number of caps misplaced. A lower score indicates improved color discrimination ability. A negative change from baseline indicates an improvement in symptoms.

End point type	Secondary
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End point timeframe:

Baseline; Week 48 and Week 96

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End point values	GS010 treatment	Sham comparator		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24 <sup>[13]</sup>	25 <sup>[14]</sup>		
Units: total error score				
arithmetic mean (standard deviation)				
Week 48	-30.0 (± 255.0)	-44.3 (± 182.2)		
Week 96	-10.3 (± 247.3)	-61.0 (± 188.9)		

Notes:

[13] - Week 48 N = 24

Week 96 N = 23

[14] - Week 48 N = 25

Week 96 N = 24

### Statistical analyses

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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)

Adverse event reporting additional description:

Because participants received both treatment and sham procedure simultaneously, adverse events (AEs) are reported overall for systemic and ocular AEs. Reported events include AEs associated with sham procedure.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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### Reporting groups

Reporting group title	All participants
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Reporting group description:

All participants who were randomized and received study treatment, GS010 and Sham.

Serious adverse events	All participants		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 37 (8.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal tear	Additional description: This event occurred only in an eye receiving the sham procedure.		
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	1 / 37 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			



Diverticulitis			
subjects affected / exposed	1 / 37 (2.70%)		
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 %

<b>Non-serious adverse events</b>	All participants		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 37 (100.00%)		
Investigations			
Gamma-glutamyl transferase increased			
subjects affected / exposed	8 / 37 (21.62%)		
occurrences (all)	11		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 37 (10.81%)		
occurrences (all)	8		
Paraesthesia			
subjects affected / exposed	2 / 37 (5.41%)		
occurrences (all)	2		
Immune system disorders			

Drug hypersensitivity subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Social circumstances Alcohol use subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Eye disorders Anterior chamber cell subjects affected / exposed occurrences (all)	9 / 37 (24.32%) 11		
Autoimmune uveitis subjects affected / exposed occurrences (all)	Additional description: The verbatim AE term is "intermediate uveitis". 1/14 affected participants experienced this event only in sham-treated eyes. 14 / 37 (37.84%) 15		
Cataract subjects affected / exposed occurrences (all)	Additional description: 1/4 affected participants experienced this event only in sham-treated eyes 4 / 37 (10.81%) 4		
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	Additional description: 3/6 affected participants experienced this event only in sham-treated eyes. 6 / 37 (16.22%) 7		
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	6 / 37 (16.22%) 7		
Dry eye subjects affected / exposed occurrences (all)	Additional description: 1/2 affected participants experienced this event only in sham-treated eyes. 2 / 37 (5.41%) 3		
Iridocyclitis subjects affected / exposed occurrences (all)	Additional description: 1/15 affected participants experienced this event only in sham-treated eyes. 15 / 37 (40.54%) 17		
Iritis subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Keratic precipitates subjects affected / exposed occurrences (all)	13 / 37 (35.14%) 16		

Eye pain	Additional description: 1/3 affected participants experienced this event only in sham-treated eyes.		
	subjects affected / exposed	3 / 37 (8.11%)	
	occurrences (all)	4	
Intraocular pressure increased	Additional description: 1/11 affected participants experienced this event only in sham-treated eyes.		
	subjects affected / exposed	11 / 37 (29.73%)	
	occurrences (all)	13	
Vitritis	subjects affected / exposed	6 / 37 (16.22%)	
	occurrences (all)	6	
Vitreous floaters	subjects affected / exposed	2 / 37 (5.41%)	
	occurrences (all)	3	
Vitreous detachment	subjects affected / exposed	2 / 37 (5.41%)	
	occurrences (all)	2	
Vitreous cells	Additional description: 1/7 affected participants experienced this event only in sham-treated eyes.		
	subjects affected / exposed	7 / 37 (18.92%)	
	occurrences (all)	7	
Visual impairment	subjects affected / exposed	3 / 37 (8.11%)	
	occurrences (all)	3	
Punctate keratitis	Additional description: 4/15 affected participants experienced this event only in sham-treated eyes.		
	subjects affected / exposed	15 / 37 (40.54%)	
	occurrences (all)	17	
Gastrointestinal disorders			
Abdominal pain upper	subjects affected / exposed	2 / 37 (5.41%)	
	occurrences (all)	2	
Psychiatric disorders			
Depression	subjects affected / exposed	2 / 37 (5.41%)	
	occurrences (all)	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 37 (16.22%) 9		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2015	<p>In Global Revision 1, the protocol was revised to incorporate the following:</p> <ol style="list-style-type: none"><li>1. Added newly determined names of the current studies (RESCUE and REVERSE) to the protocol.</li><li>2. Updated the clinical and nonclinical safety profile of GS010.</li><li>3. The objectives, endpoints, and statistical analyses were revised to harmonize with Protocol GS-LHON-CLIN-03A.<ol style="list-style-type: none"><li>a. The primary endpoint was to be the ETDRS score at 48 weeks compared to Baseline.</li><li>b. 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.</li></ol></li><li>4. Randomization was revised from the better-seeing eye to the right eye of each participant randomized with the left receiving the alternative.</li><li>5. Revised the randomization and unmasking methods from envelopes to an interactive voice recognition system.</li><li>6. Respiratory rate was removed from the measured vital signs.</li><li>7. Applanation tonometry was further specified as Goldmann applanation tonometry.</li><li>8. The color vision test was changed from the 15-Hue color test to the Farnsworth Munsell 100 Hue Color Test.</li><li>9. Added a section for Study Duration with a definition of EOS as last participant's last visit.</li><li>10. The data collected by the SD-OCT assessment were simplified.</li><li>11. More specific time frames were assigned to some secondary endpoints.</li><li>12. Added color fundus photos at Visit 1 for Baseline and Visits 4 to 12 as necessary if the participant had vitreous inflammation.</li><li>13. Added all vision-related testing to Visit 1.</li><li>14. Specific instructions were added on establishing and maintaining the study masking and procedures for unmasking.</li><li>15. The timing of the primary analysis was revised so that the primary efficacy analysis can be performed after all participants complete Week 48.</li><li>16. Changed the term "patients" to "subjects" when referring to study participants.</li></ol>
23 February 2016	<p>In Global Revision 2, the protocol was revised to incorporate the following:</p> <ol style="list-style-type: none"><li>1. Added the ClinicalTrials.gov identifier for the trial.</li><li>2. Made refraction for BCVA required at each study follow-up visit regardless of change in visual acuity.</li><li>3. Required ND4 genotyping to be performed for all participants in an appropriately certified central study laboratory.</li><li>4. Clarified in the Schedule of Events that QoL questionnaires should be administered before visual acuity tests were conducted.</li><li>5. Clarified the non-selection criteria with regard to participants with well-controlled glaucoma.</li><li>6. Updated the appropriate post-reconstitution storage conditions for the investigational product.</li><li>7. Clarified the appropriate site personnel who could randomize participants.</li><li>8. Widened eligible participants age range to include paediatric participants aged 15 to 18 years and made corresponding changes to the informed consent process to include paediatric participants.</li></ol>

07 November 2016	<p>In Global Revision 3, the protocol was revised to incorporate the following:</p> <ol style="list-style-type: none"> <li>1. Updated the job title of one of the study Sponsor contacts.</li> <li>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.</li> <li>3. Clarified how the duration of vision loss should be calculated for the purpose of determining study eligibility.</li> <li>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.</li> </ol>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported