



## Clinical trial results:

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

#### Summary

EudraCT number	2017-002153-11
Trial protocol	DE GB IT FR
Global end of trial date	25 May 2022

#### Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

#### Trial information

##### Trial identification

Sponsor protocol code	GS-LHON-CLIN-06
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03406104
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Gensight Biologics
Sponsor organisation address	74 Faubourg Saint Antoine, Paris, France, 75012
Public contact	Szilvia Fabian, Gensight Biologics, sfabian@GENSIGHT-BIOLOGICS.COM
Scientific contact	Magali Tael, Gensight Biologics, mtael@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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2022
Global end of trial reached?	Yes
Global end of trial date	25 May 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	62
EEA total number of subjects	26

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)	7
Adults (18-64 years)	55
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial recruited subjects previously treated with GS010 and Sham during 2 Phase III studies—RESCUE and REVERSE. The study followed subjects for an additional 3 years, for a total of 5 years post-injection. The study included 5 visits at 2, 2.5, 3, 4, and 5 years after the investigational medicinal product (IMP) injection.

### Pre-assignment

Screening details:

Not applicable as no screening period

### Period 1

Period 1 title	from 2 to 5 Years (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	GS010 arm

Arm description:

Subjects with Leber Hereditary Optic Neuropathy (LHON) who participated in the RESCUE and REVERSE clinical trials were administered gene therapy with the investigational medicinal product (IMP), GS010, by a single intravitreal (IVT) injection in a single randomly-selected eye, while the fellow eye received a sham IVT injection.

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

Dosage and administration details:

GS010 (rAAV2/2-ND4) Drug Product is a sterile suspension of concentrated and purified virus vector formulated in Balanced Saline Solution (BSS) plus 0.001% Pluronic F68®. GS010 is stored at  $\leq -70^{\circ}\text{C}$ . GS010 was administered via standard intravitreal injection under local (i.e. topical) anesthesia.

Investigational medicinal product name	Sham injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraocular use

Dosage and administration details:

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.

<b>Arm title</b>	Sham IVT arm
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Arm description:

Subjects with Leber Hereditary Optic Neuropathy (LHON) who participated in the RESCUE and REVERSE clinical trials were administered gene therapy with the investigational medicinal product (IMP), GS010, by a single intravitreal (IVT) injection in a single randomly-selected eye, while the fellow eye received a sham IVT injection.

Arm type	sham injection
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	GS010 arm	Sham IVT arm
Started	31	31
Completed	28	27
Not completed	3	4
Adverse event, serious fatal	2	-
Consent withdrawn by subject	-	2
Covid	1	-
Lost to follow-up	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	from 2 to 5 Years
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Reporting group description: -

Reporting group values	from 2 to 5 Years	Total	
Number of subjects	62	62	
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)	7	7	
Adults (18-64 years)	55	55	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	35.9		
standard deviation	± 15.3	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	49	49	

### Subject analysis sets

Subject analysis set title	Modified Intent-to-treat population
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All efficacy analyses were conducted on the modified intent-to-treat population and additionally in subset populations, as appropriate. The modified intent-to-treat (mITT) population consisted of all subjects who received the IMP in

RESCUE or REVERSE Phase III studies, consented to be enrolled in this LTFU study, and provided visual acuity data at Visit 2 (Year 2.5).

Reporting group values	Modified Intent-to-treat population		
Number of subjects	62		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	7		
Adults (18-64 years)	55		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			

## End points

### End points reporting groups

Reporting group title	GS010 arm
Reporting group description: Subjects with Leber Hereditary Optic Neuropathy (LHON) who participated in the RESCUE and REVERSE clinical trials were administered gene therapy with the investigational medicinal product (IMP), GS010, by a single intravitreal (IVT) injection in a single randomly-selected eye, while the fellow eye received a sham IVT injection.	
Reporting group title	Sham IVT arm
Reporting group description: Subjects with Leber Hereditary Optic Neuropathy (LHON) who participated in the RESCUE and REVERSE clinical trials were administered gene therapy with the investigational medicinal product (IMP), GS010, by a single intravitreal (IVT) injection in a single randomly-selected eye, while the fellow eye received a sham IVT injection.	
Subject analysis set title	Modified Intent-to-treat population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All efficacy analyses were conducted on the modified intent-to-treat population and additionally in subset populations, as appropriate. The modified intent-to-treat (mITT) population consisted of all subjects who received the IMP in RESCUE or REVERSE Phase III studies, consented to be enrolled in this LTFU study, and provided visual acuity data at Visit 2 (Year 2.5).	

### Primary: Ocular Adverse Events (AEs)

End point title	Ocular Adverse Events (AEs) <sup>[1]</sup>
End point description: Number of Eyes with Ocular Adverse events related to study treatment or study procedures as judged by the investigator reported from year 2 to year 5 post treatment	
End point type	Primary
End point timeframe: from 2 to 5 years	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive statistical analyses.	

End point values	GS010 arm	Sham IVT arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: number of eyes	5	1		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Visual Acuity

End point title	Visual Acuity
End point description: Change from Nadir to 5 Years post-treatment, Assessed at Baseline in RESCUE and REVERSE studies to	



year 5 post-treatment, expressed in LogMAR.

On chart visual acuity: Visual acuity inferior or equal to LogMAR +1.6

Off chart visual acuity: Visual acuity superior to LogMar +1.7

Normal vision LogMar: 0 and less than 0

End point type	Secondary
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End point timeframe:

Nadir to 5 Years post-treatment, Assessed at Baseline in RESCUE and REVERSE studies to year 5 post-treatment

End point values	GS010 arm	Sham IVT arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: LogMar				
arithmetic mean (standard deviation)	-0.44 (± 0.46)	-0.39 (± 0.36)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Responder Analysis: clinically relevant recovery

End point title	Responder Analysis: clinically relevant recovery
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End point description:

CRR clinically relevant recovery from Nadir defined as i/ for eyes on chart at Nadir, an improvement of at least -0.2 LogMar from Nadir and ii/ for eyes off chart at Nadir eyes that became on chart.

Off chart visual acuity expressed in LogMar: more than +1.7

On chart visual acuity expressed in LogMar: less than 1.6

Normal vision LogMar: 0 and less than 0

End point type	Secondary
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End point timeframe:

Nadir to 5 Years post-treatment, Assessed at Baseline in RESCUE and REVERSE studies to year 5 post-treatment

End point values	GS010 arm	Sham IVT arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: percentage of eye	60	66		

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Eyes on chart**

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End point title	Eyes on chart
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End point description:

Definition: visual acuity inferior or equal to LogMar +1.6 at 5 Years post-treatment

End point type	Secondary
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End point timeframe:

Year 5 post-treatment

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End point values	GS010 arm	Sham IVT arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: percentage of eyes	76	79		

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

from 2 to 5 years

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	All subjects
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Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 62 (12.90%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma multiforme			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm progression			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
hip fracture			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Humerus fracture			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
appendicitis perforated			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pneumonia			
subjects affected / exposed	1 / 62 (1.61%)		
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 subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 62 (30.65%)		
Investigations			
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Eye disorders			
Cataract			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	13		
Intraocular Pressure Increased			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	8		
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 September 2018	<p>Purposes and Rationale for Amendment</p> <ol style="list-style-type: none"><li>1. Based on REVERSE (Study GS-LHON-CLIN-03B) available efficacy data, contrast sensitivity measured with the Pelli-Robson chart constitutes additional and complementary key information to better assess patients' benefit from GS010. Therefore, contrast sensitivity assessments have been added every year through the GS-LHON-CLIN-06 long-term follow up study.</li><li>2. Another purpose of the amendment is to add comparisons between all GS010-treated eyes and all sham-treated eyes at years 2, 2.5, 3, 4, and 5 for the secondary endpoints "visual improvement as measured by LogMAR" and "change of ganglion cell layer thickness/volume and topographical map and other parameters measured by SD-OCT." The addition of these comparisons will make the efficacy analysis more complete and provide additional insight into the long-term efficacy of GS010.</li></ol>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported