



# Corporate Presentation

October 2021

A LEADING Gene Therapy BIOTECHNOLOGY COMPANY

[GENSIGHT-BIOLOGICS.COM](https://www.gensight-biologics.com)

# Disclaimer

This document contains forward-looking statements and estimates made by the GenSight Biologics S.A. (the “Company”), including with respect to the anticipated future performance of the Company, its subsidiaries and affiliates, and the market in which they operate. They include all matters that are not historical facts. These forward-looking statements can be identified by the use of forward-looking terminology including the terms “developments,” “estimates,” “expects,” “intends,” “may,” “milestones,” “potential,” “value,” “time to market,” “targeting,” “on track,” “planned,” “will,” “move to,” or other variations or comparable terminology, or by discussions of strategy and funding, as well as the Company’s, its subsidiaries’ and affiliates’ technology, and are based on financial and non-financial information, including projections as to the future regulatory situation and other information and assumptions. Such statements, forecasts and estimates are based on various assumptions and assessments of known and unknown risks, uncertainties and other factors, which were deemed reasonable when made but may or may not prove to be correct. Actual events are difficult to predict and may

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# Corporate Overview – Transitioning from R&D to Commercial Organization

## GenSight at the forefront of Gene Therapy in Ophthalmology

- Publicly traded Biotech company
- Seasoned management team with strong BioPharma and Financial markets experience
- Differentiated gene therapy approach forming a technology platform leveraging disruptive gene therapies in ophthalmology and broader
  - Lead product (LUMEVOQ) targets mitochondrial disease
  - Second compound (GS030) uses optogenetic technology

## LUMEVOQ® – Filed for Approval in Europe in September 2020 and preparing for commercial launch in H1 2022

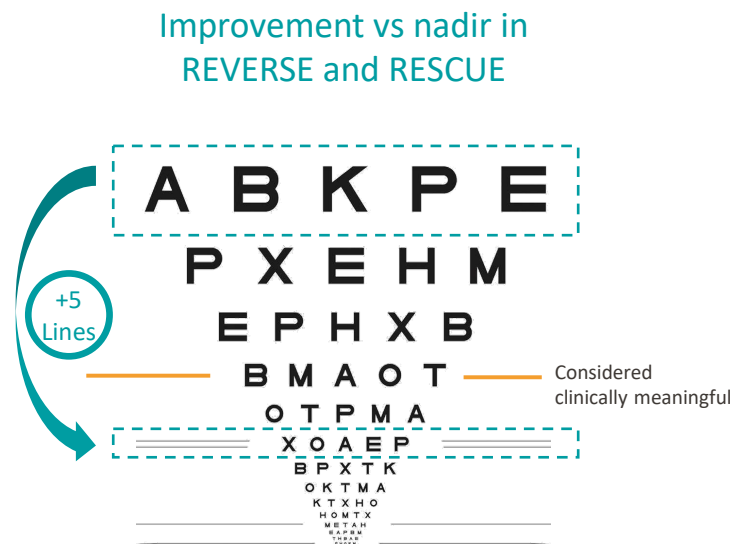
- Market:** High unmet medical need; 1,200 – 1,500 new patients / yr EU + US
- Efficacy:** Unparalleled clinical benefit demonstrated in two Phase III studies
  - +28/+26 ETDRS letters (i.e. over 5 lines on visual scale) improvement vs nadir(1)
- Durability & Safety:** Excellent tolerability; Visual improvement maintained at least 3 years post-treatment
  - Clinically meaningful improvement on all Quality of Life parameters at week 96
- Disease modifying:** Stark difference from Natural History

## Commercial strategy and manufacturing capabilities close to completion

- Bilateral injection priced at €700,000 / patient in French named patient Temporary Authorization for Use

(1) Nadir: worst visual acuity from baseline

Established in 2012 / IPO in 2016	
EuroNext Paris:	SIGHT
Market Cap (May 3, 2021):	€ 423m
Avg 30-day Daily volume:	1.0% of O/S
Cash (June 30, 2021):	€ 54.3 m



# Seasoned Executive Team



**Bernard Gilly**  
*Chief Executive Officer*

**PIXIUM VISION** (Since 2011)  
**FOVEA PHARMA** (2005-2009)  
**SOFINNOVA PARTNERS** (2000-2005)  
**TRANSGENE** (1992-2000)  
Ph.D. in biology and bio-economics



**Thomas Gidoin**  
*Chief Financial Officer*

**DBV TECHNOLOGIES** (2012-2015)  
**IPSEN** (2008-2011)  
**ERNST & YOUNG** (2007-2008)



**Magali Taiel**  
*Chief Medical Officer*

**ProQR THERAPEUTICS** (2016-2018)  
**ELI LILLY** (2004-2016)  
**PFIZER** (2001-2004)  
**SERVIER** (1999-2001)  
M.D., Board-certified ophthalmologist



**Leigh Shaw**  
*VP of Regulatory Affairs*

**UNITED NEUROSCIENCE** (2017-2020)  
**NIGHTSTARX** (2015-2017)  
**GREGORY FRYER ASSOCIATES** (2005-2015)  
**HUNTINGDON LIFE SCIENCES** (2002-2005)  
**CANTAB PHARMACEUTICALS** (1995-2001)



**Catherine Cancian**  
*VP of Pharmaceutical Operations*

**GENETHON** (2015-2017)  
**SANOFI PASTEUR** (1998-2014)



**Julio Benedicto**  
*VP of Marketing*

**IMS CONSULTING** (2011-2017)  
**BOOZ & COMPANY** (2010-2011)  
**MONITOR GROUP** (1994-2009)



**Marie-Claude Holtz**  
*VP of Quality*

**EXELTIS SANTE** (2016-2019)  
**PFIZER** (2015-2016)  
**ABBVIE** (2014-2015)  
**GALDERMA** (2012-2013)  
**LABORATOIRE LAFON (TEVA)** (1993-2012)  
Pharm.D.



**Marion Ghibaudo**  
*Chief Technical Officer*

**MAUNA KEA TECHNOLOGIES** (2018-2021)  
**L'OREAL** (2009-2018)  
PhD in biophysics



**Isabelle Scarabin**  
*Director, Business Development*

**LYONBIPOLE** (2006-2013)  
**GREATER LYON** (2002-2006)  
**RESSOURCES EN INNOVATION** (1999-2002)  
**SANOFI PASTEUR MSD** (1998-1999)

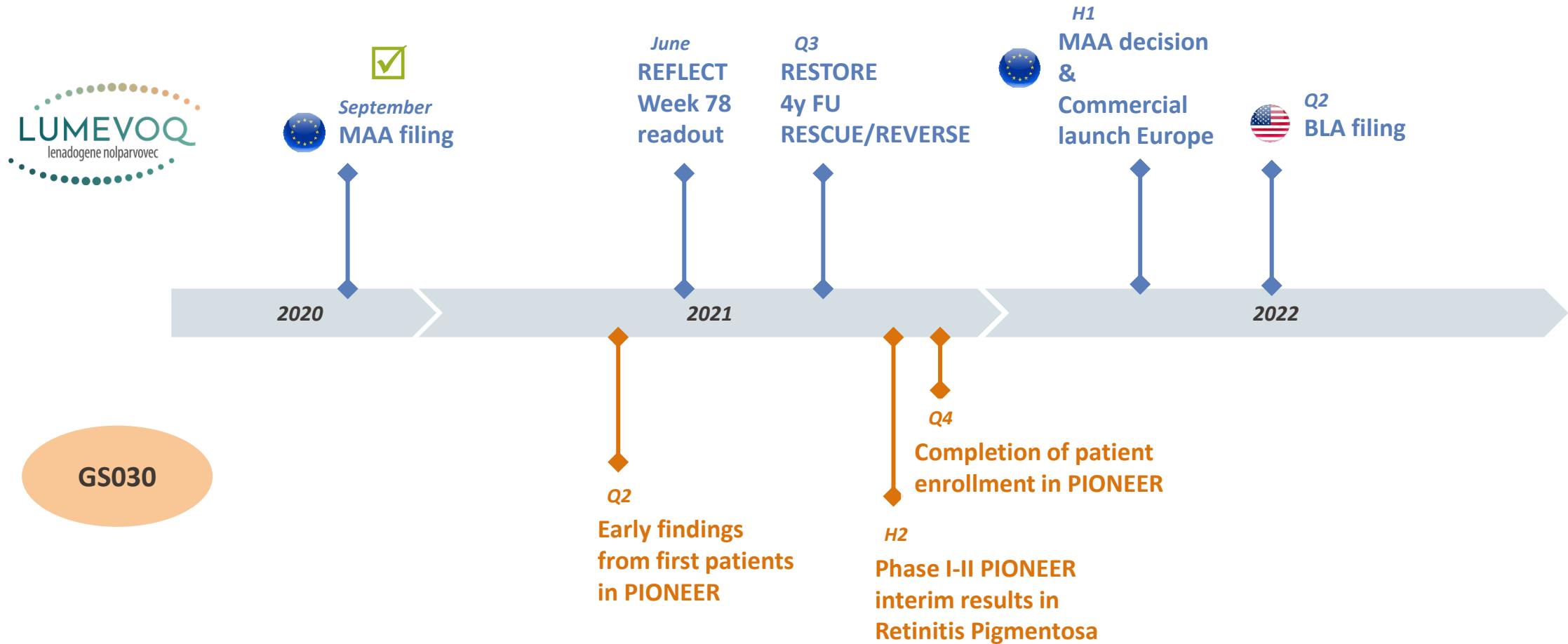
# Pipeline: solid and advanced product portfolio in ophthalmic Gene Therapy

Technology	Product Candidate	Indication	Research	Preclinical	Phase I/II	Phase III	Registration	Expected Approval	
MTS platform	LUMEVOQ® (FDA & EMA Orphan Drug Designation)	LHON ND4 (EU)						H1 2022	<b>REVERSE:</b> Phase III top-line data reported in Apr (48w) & Oct (72w) 2018 and in May 2019 (96w)
		LHON ND4 (US)						Q2 2022	<b>RESCUE:</b> Phase III top-line data reported in Feb (48w), Apr (72w) and Sep (96w) 2019
									<b>REFLECT*:</b> Phase III top-line data (78w) reported in June 2021
	GS011	LHON ND1							Initiate preclinical studies following GS010 Phase III clinical data
	Undisclosed Mitochondrial Target	Undisclosed							
Optogenetics	GS030 (FDA & EMA Orphan Drug Designation)	Retinitis Pigmentosa (RP)							<b>PIONEER:</b> Extension cohort in PIONEER Phase I/II clinical trial to be completed by end 2021. Early findings in Q2 2021
	GS030	Dry AMD & Geographic Atrophy							

\*Conducting this trial under a special protocol assessment with the FDA

**LUMEVOQ® commercial launch in Europe expected in H1 2022**

# Rich upcoming news flow with numerous inflexion points



# LUMEVOQ® (GS010) in LHON-ND4

Last Phase III ongoing in Leber Hereditary Optic Neuropathy

Commercial preparation ongoing for 2022 European launch

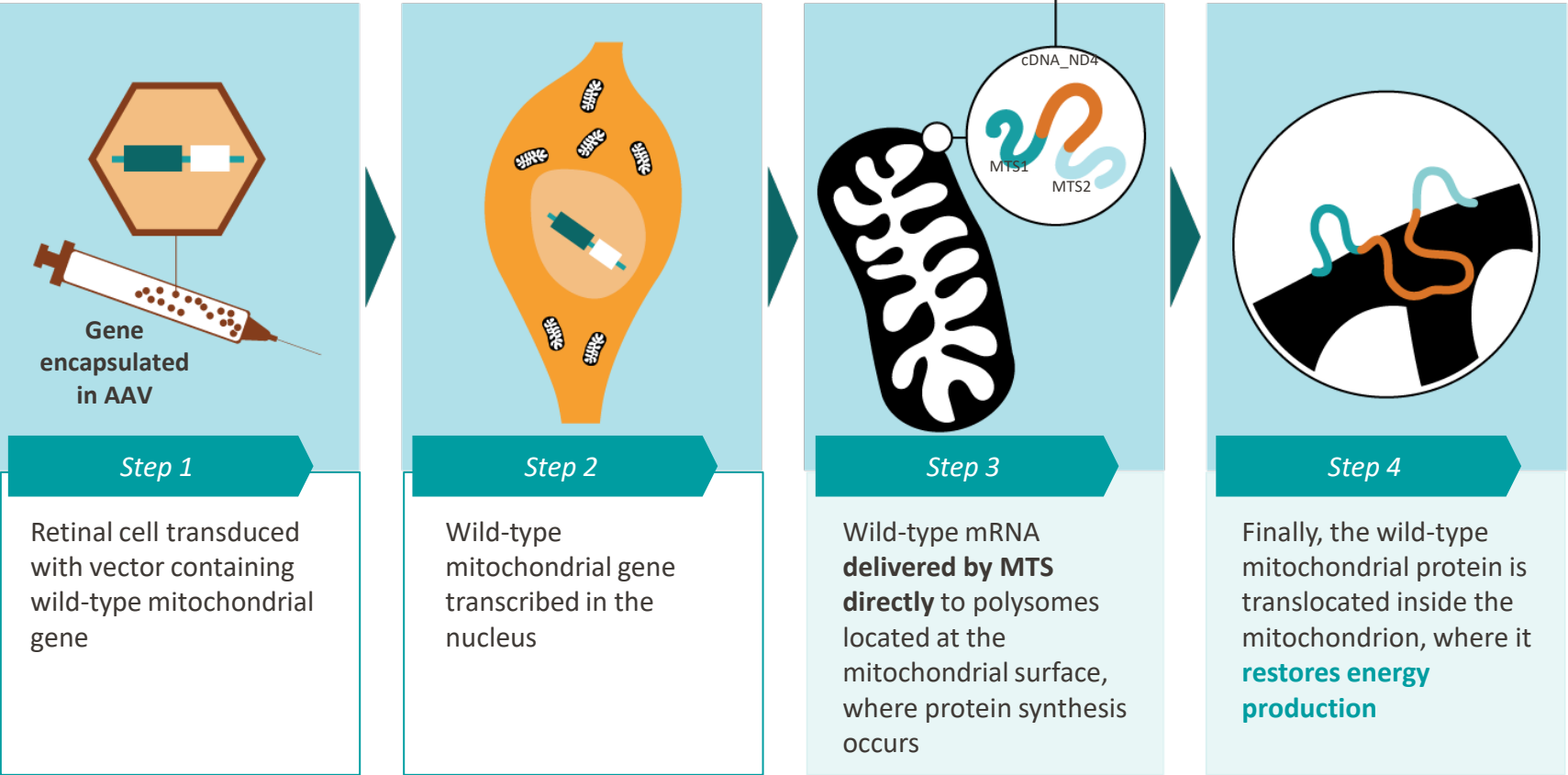
A stylized, light teal graphic of a DNA double helix is positioned in the lower half of the slide, extending from the left edge towards the right. It features two curved lines representing the sugar-phosphate backbones, connected by several vertical lines representing the nitrogenous base pairs.



# LUMEVOQ® introduces Gene Therapy solution

Replacing affected mitochondrial mRNA via proprietary *MTS\** technology

*MTS in action for GS010:*



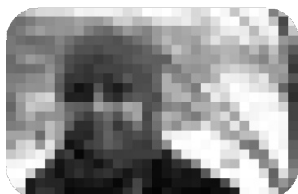
\*MTS = mitochondrial targeting sequence



# Leber Hereditary Optic Neuropathy (LHON-ND4) high unmet medical need

## What is LHON-ND4

- Rare inherited mitochondrial disease leading to degeneration of retinal ganglion cells (RGCs) and their axons, most often leading to **sudden loss of central vision**
- Sudden loss typically occurs at age 15-35, mostly in men
- **97%** of patients have bilateral involvement < 1 year / 25% of cases are simultaneous
- 90% of LHON patients have genes **MT-ND4** (~75% in **US/EU**), MT-ND1 and/or MT-ND6 affected



Incidence (new cases per year)

~800-1,200

Prevalence

~15,000-22,000

## Progressive disease

- Rare recovery from vision **nadir**<sup>(1)</sup> reached during acute phase

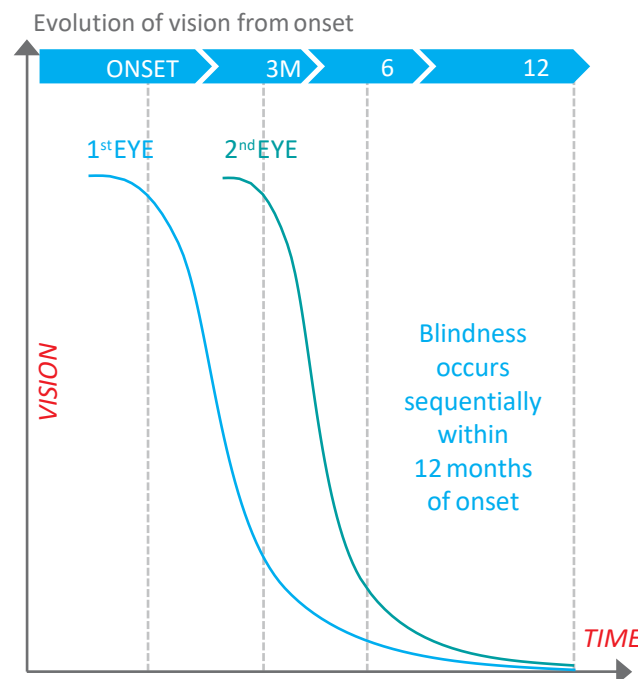


Image source: illustrated from Newman NJ et al., Am J Ophthalmol. 141(6), 1061-1067, 2006

## Current treatment paradigm

- No cure for LHON-ND4
- Low-vision aids are primary supportive care
- Santhera's Raxone EU approved (under exceptional circumstances) in 2015 with mechanism of action partially relying on bypassing the dysfunctional complex I of the mitochondrial respiratory chain
  - Approved based on Phase 2 data, Phase 4 ongoing
  - Demonstrated **3 letters improvement** vs placebo ( $p=0.291$  / NS) at week 24 in Best recovery of Visual Acuity (primary)<sup>(2)</sup>
  - Demonstrated **6 letters improvement** vs placebo ( $p=0.078$  / NS) at week 24 in Change in best Visual Acuity<sup>(2)</sup>

(1) Nadir: worst visual acuity from baseline

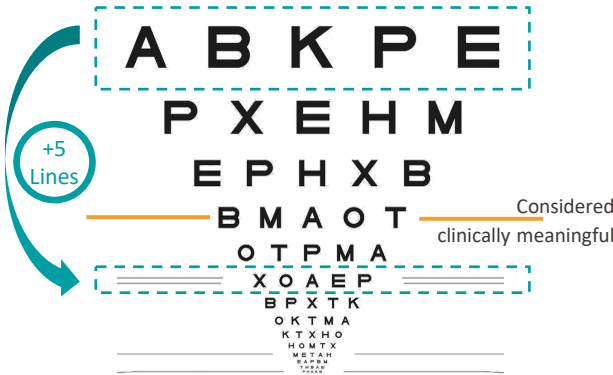
(2) Raxone European full prescribing information [https://www.ema.europa.eu/en/documents/product-information/raxone-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/raxone-epar-product-information_en.pdf)

# Unparalleled clinical benefit demonstrated with LUMEVOQ® (GS010) in LHON in two Phase III studies

5 lines bilateral improvement of visual acuity



Change from NADIR in ETDRS letter equivalents		
Week 96		
	n	Mean (SD)
All-GS010 eyes	37	+28.3 (22.5)
All-sham eyes	37	+24.5 (24.0)



Change from NADIR in ETDRS letter equivalents		
Week 96		
	n	Mean (SD)
All-GS010 eyes	34	+26.3 (23.9)
All-sham eyes	34	+22.8 (24.2)

76% of REVERSE subjects achieved at least 15 letters improvement vs nadir in one or two eyes

71% of RESCUE subjects achieved at least 15 letters improvement vs nadir in one or two eyes

- +28/+26 ETDRS letters (i.e. over 5 lines on visual scale) bilateral improvement vs nadir
- Stark difference from natural history outcome
- 70+% of patients are gaining 15 letters or more
- Effect is maintained at least 3 years post administration
- Favorable safety profile

NADIR is defined as the **worst** BCVA from baseline to Week 96  
Mean change from nadir was calculated using observed values (no data imputation)

# Other data complement the finding on sustained bilateral improvement



## Insights on Mechanism of Bilateral Effect

- Non-human primate study detected/quantified GS010 viral vector DNA in many tissue samples from contralateral (uninjected) eye



## Excellent Tolerability

- No serious adverse events in LUMEVOQ<sup>®</sup>-treated eyes, and no discontinuation due to ocular events
- Most frequently seen ocular adverse events in LUMEVOQ<sup>®</sup>-treated eyes were mainly related to the injection procedure
- Main ocular AE : mild intraocular inflammation – responsive to conventional treatment and without sequelae

# Indirect comparison as a cornerstone for EMA Filing

## External control group needed because of bilateral improvement in RESCUE and REVERSE trials

- Contralateral effect eliminated the **control group** formed by the sham eyes, as defined in the studies' designs
- EMA scientific advice highlighted the importance of performing an indirect comparison of LUMEVOQ® data using an external control group

### Treated Group 76 patients / 152 eyes

- All patients in RESCUE, REVERSE and long-term follow-up study CLIN06 (up to the last available observation)
- Sham eyes included in the treated group, in line with the contralateral effect
  - Treated as independent observations equivalent to injected eyes

### Untreated Group (External Control) 208 patients / 408 eyes

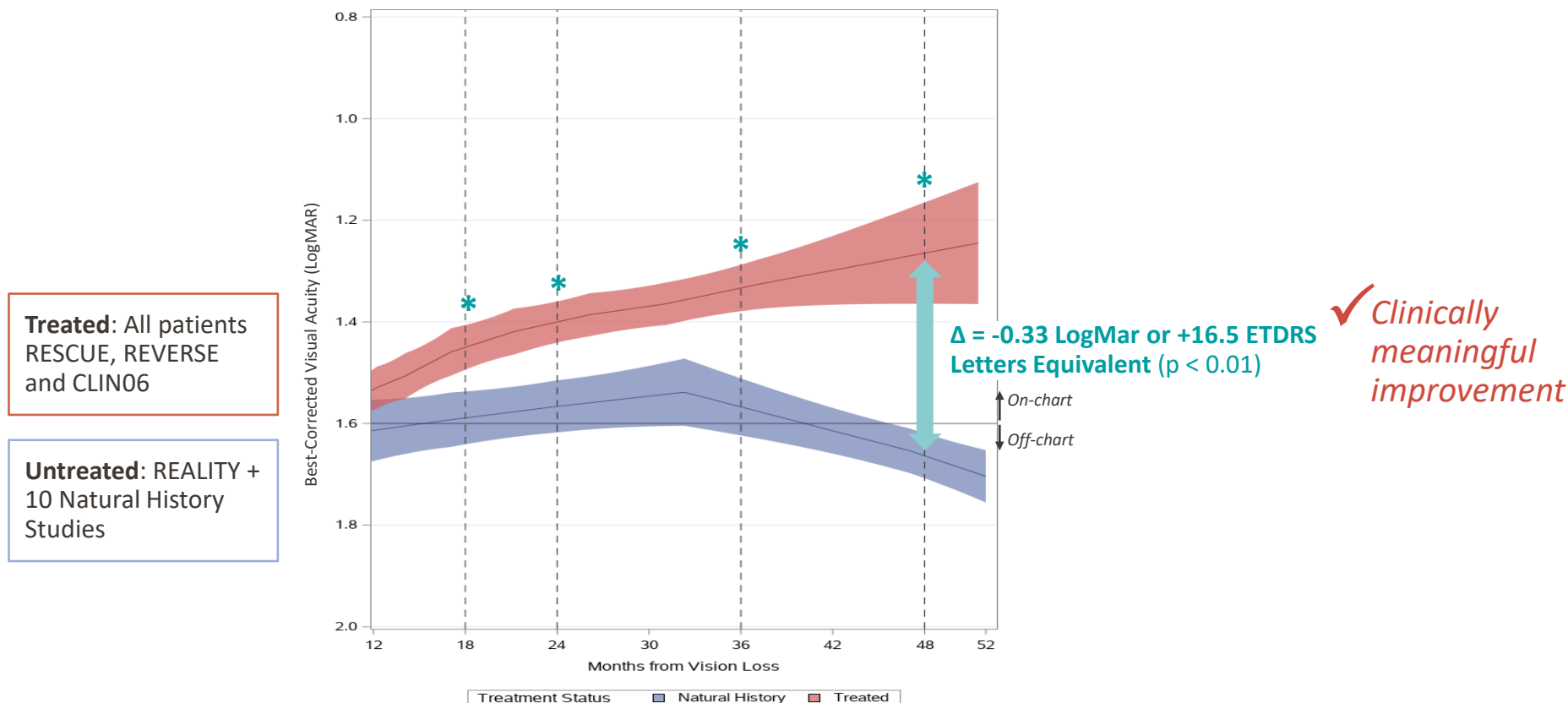
- All patients from REALITY registry study with *ND4* mutation and ≥15 years old, *and*
- Patients from 10 natural history studies (2 prospective, 8 retrospective)<sup>1</sup> identified after a systematic review of the LHON scientific literature
  - Must have individual patient data that included mutation type, age, BCVA associated with a time of onset for vision loss
  - Patients included only if they had confirmed *ND4* mutation and were ≥15 years old

<sup>1</sup>The 10 studies that passed the inclusion criteria were: Hotta 1995, Lam 2014, Nakamura 1993, Newman 1991, Qu 2007, Qu 2009, Romero 2014, Sadun 2004, Yang 2016, and Zhou 2010.

# LUMEVOQ® modifies disease outcome

Sustained improvement after LUMEVOQ® injection vs. absence of recovery among untreated patients

Figure 1. Evolution of Visual Acuity in LUMEVOQ®-treated Patients (N=76) versus Untreated Patients (N=208)



Note: All patients had a confirmed G11778A mutation in the *ND4* mitochondrial gene and were at least 15 years old. The diagram shows the Locally Estimated Scatterplot Smoothing (LOESS) curves for visual acuity in LUMEVOQ®-treated patients and untreated patients. The shaded areas represent the 95% confidence interval for the mean BCVA. "Treated" eyes refer to all eyes (LUMEVOQ® and sham) from the RESCUE, REVERSE and CLIN06 trials (N=76 patients / 152 eyes). Untreated eyes refer to patient-level data from the REALITY study and a matched data set from two prospective and eight retrospective natural history studies<sup>1</sup> (N=208 patients / 408 eyes).

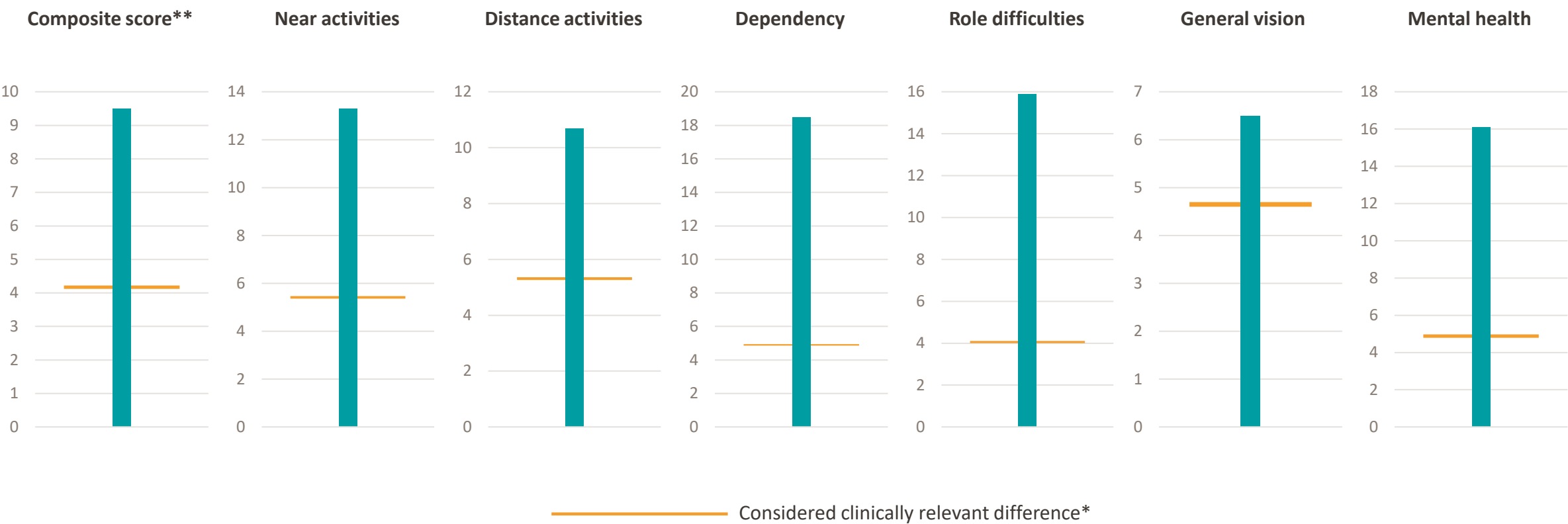
\*Statistically significant difference between mean visual acuity of treated and untreated eyes at M18, M24, M36 and M48, as illustrated by the non-overlapping confidence intervals.

# LUMEVOQ® shows meaningful improvement on Quality of Life metrics



## NEI VFQ-25 Results from REVERSE study

Mean change from baseline (absolute score) at week 96

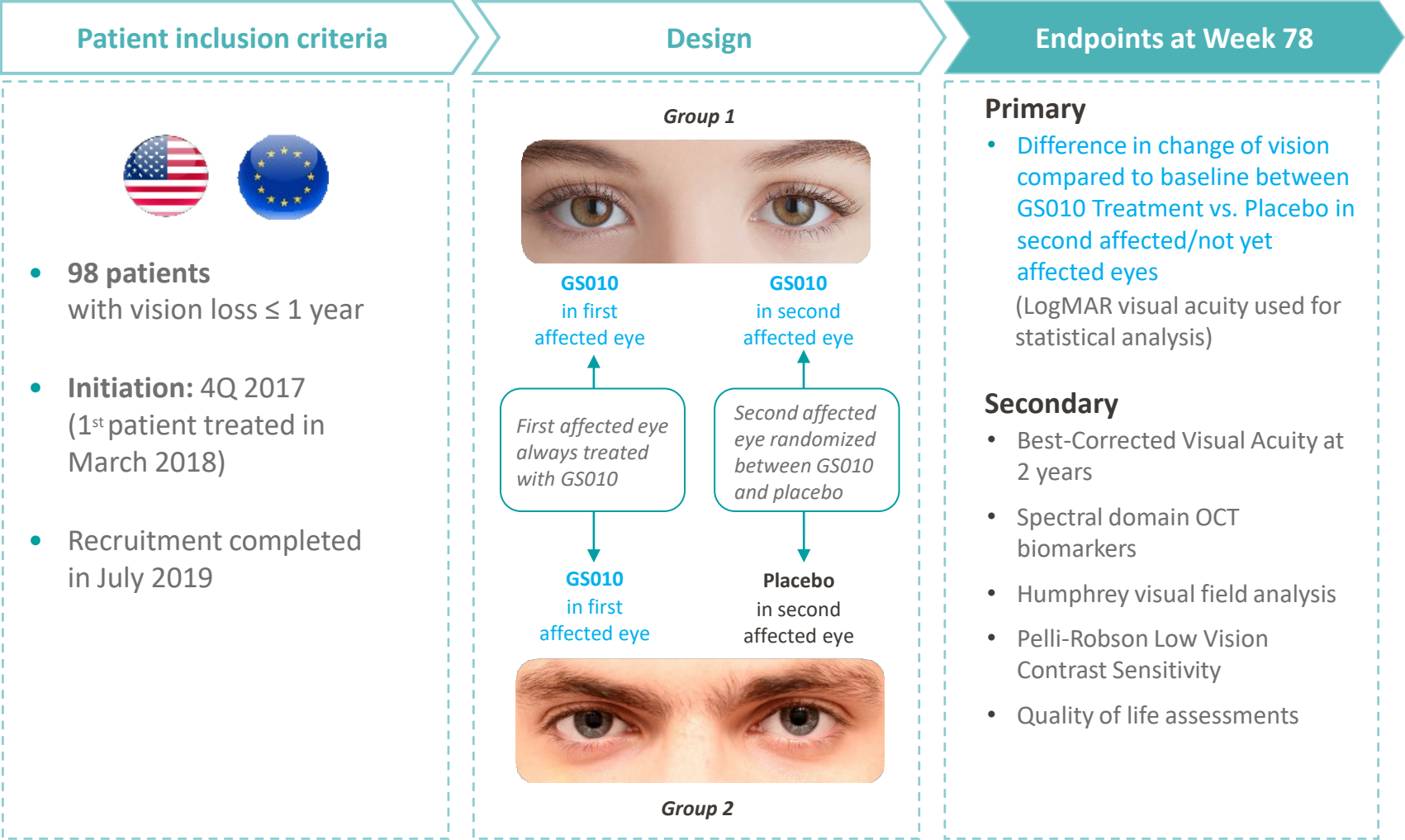
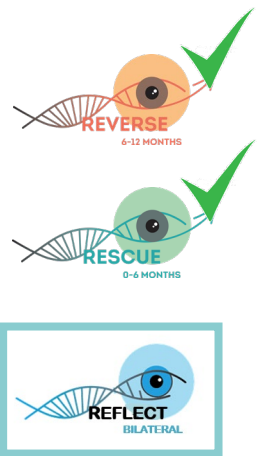


\* Suñer *et al.* (2009): clinically relevant score differences based on a clinically significant 15-letter BCVA improvement at 12 months.  
\*\* The composite score is an average of the vision-targeted sub-scale scores, excluding the general health rating question.

# Last ongoing Phase III trial: REFLECT to assess efficacy and safety of bilateral injection

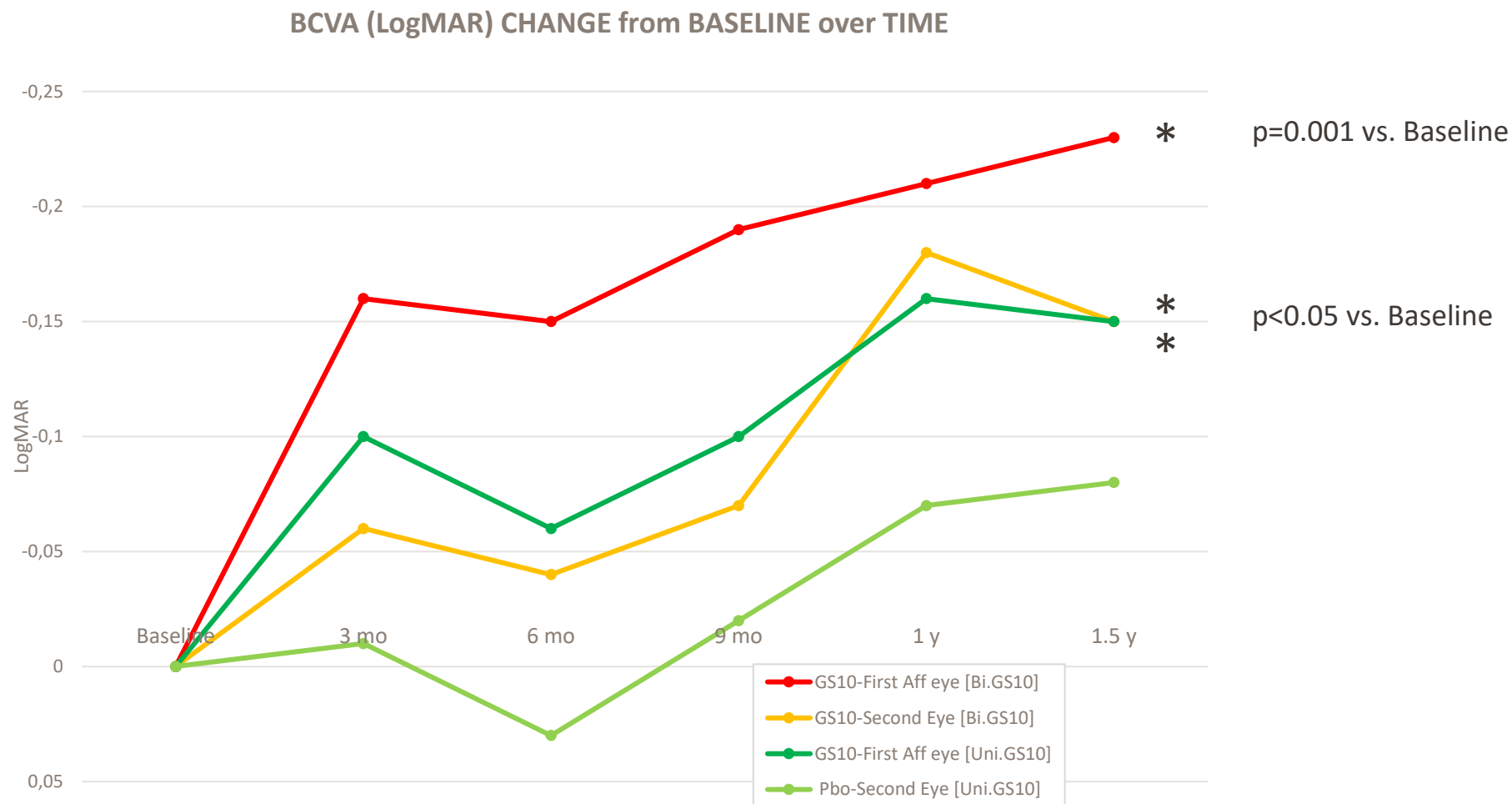
Double-masked, confirmatory study under Special Protocol Assessment from FDA

June 2021  
LUMEVOQ®  
REFLECT  
Week 78  
Read-out





# Change from Baseline of BCVA over Time



Note: treatment difference from baseline LogMAR LS means are assessed with a mixed model at the subject level, with repeated values for patient

# Change from Baseline of BCVA at 1.5 Year



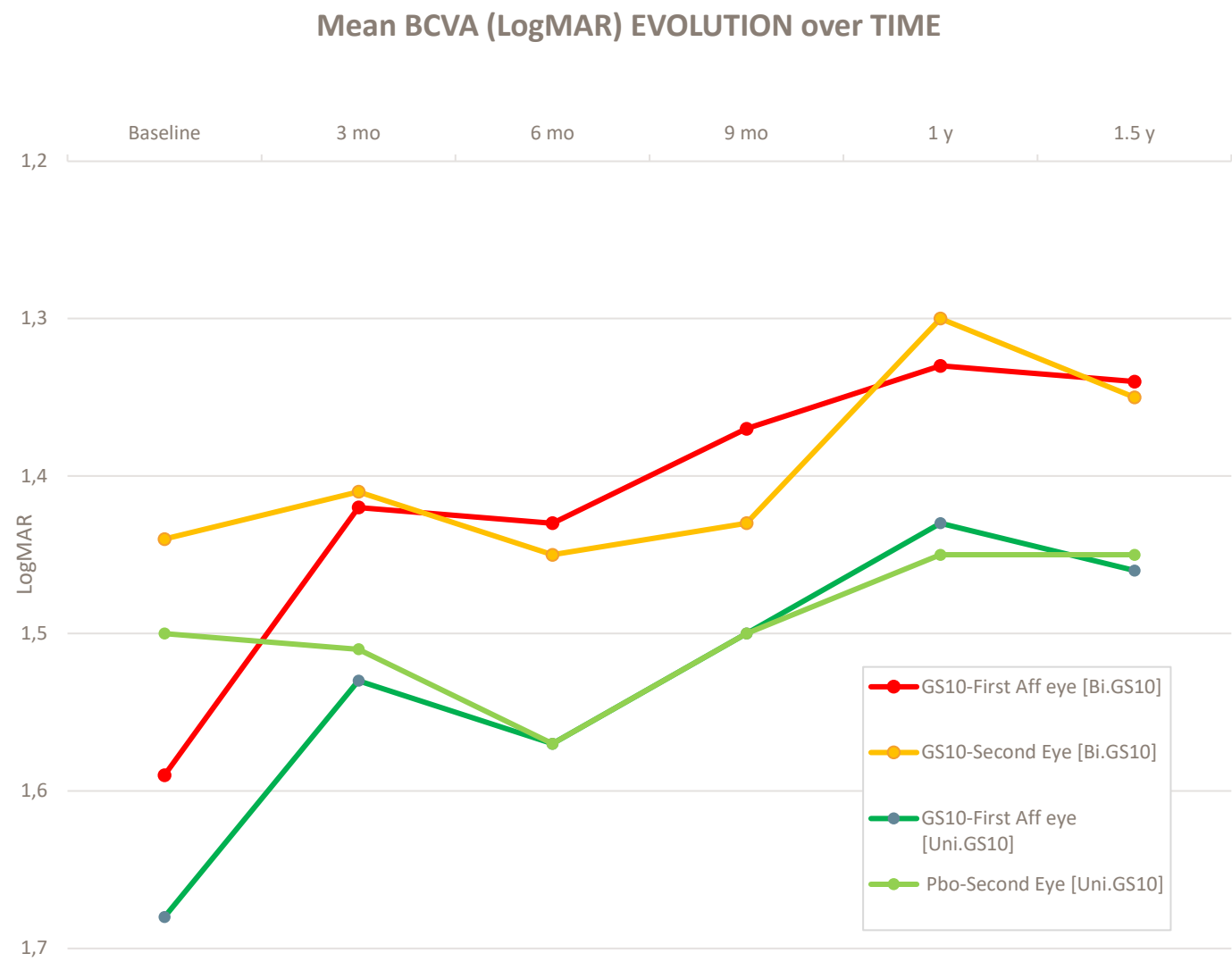
	1 <sup>st</sup> affected eye	2 <sup>nd</sup> affected eye
Subjects bilaterally injected with LUMEVOQ	LUMEVOQ -0,23 LogMAR <b>+12 ETDRS letters</b> <i>p=0.001</i>	LUMEVOQ -0,15 LogMAR <b>+8 ETDRS letters</b> <i>p&lt;0.05</i>
Subjects unilaterally injected with LUMEVOQ	LUMEVOQ -0,15 LogMAR <b>+8 ETDRS letters</b> <i>p&lt;0.05</i>	PLACEBO -0,08 LogMAR <b>+4 ETDRS letters</b> <i>p=NS</i>

# Change from Nadir of BCVA at 1.5 Year

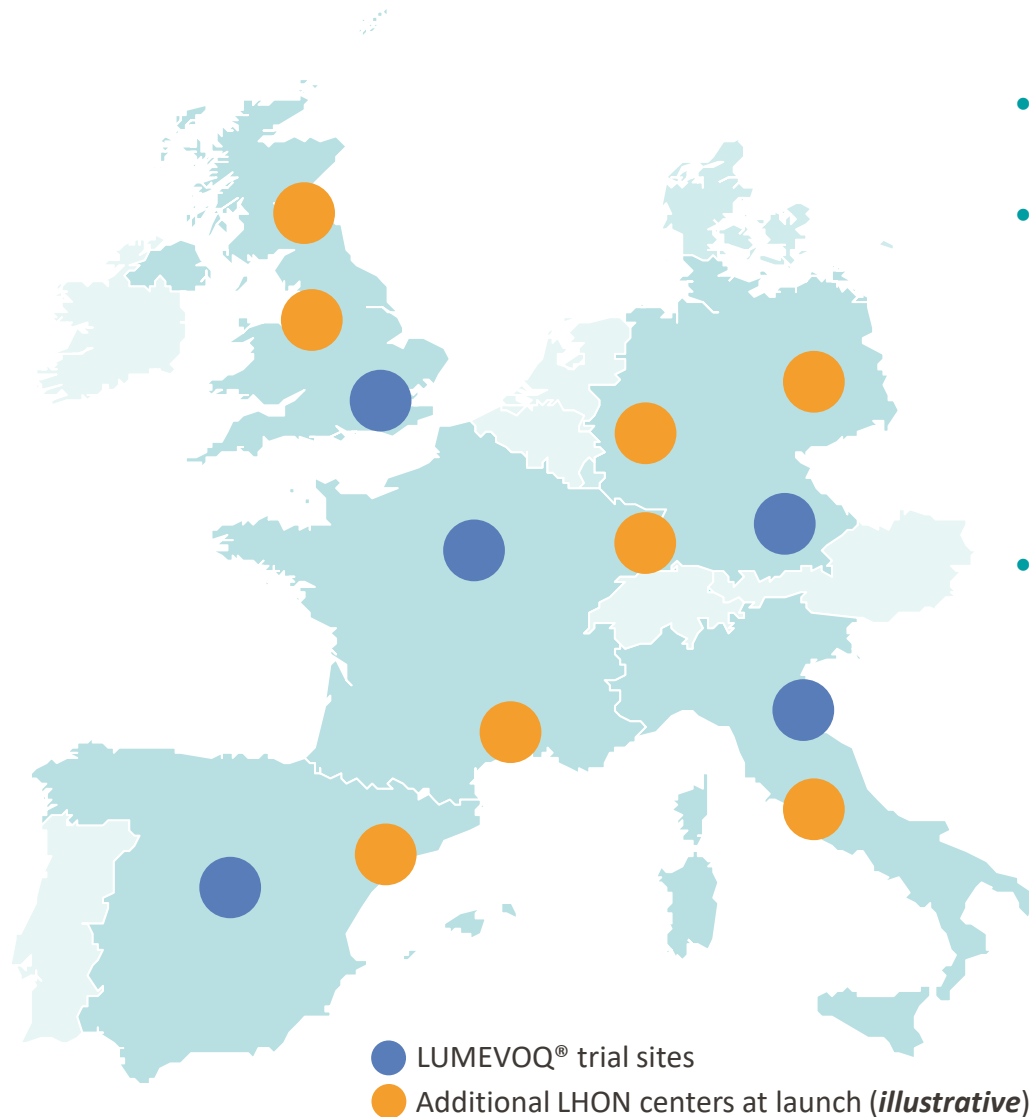


	1 <sup>st</sup> affected eye	2 <sup>nd</sup> affected eye
Subjects bilaterally injected with LUMEVOQ	LUMEVOQ -0.37 LogMAR <b>+19 ETDRS letters</b> <i>p&lt;0.0001</i>	LUMEVOQ -0.31 LogMAR <b>+16 ETDRS letters</b> <i>p&lt;0.0001</i>
Subjects unilaterally injected with LUMEVOQ	LUMEVOQ -0.37 LogMAR <b>+19 ETDRS letters</b> <i>p&lt;0.0001</i>	PLACEBO -0.25 LogMAR <b>+13 ETDRS letters</b> <i>p&lt;0.0001</i>

# EVOLUTION of BCVA over Time









# European Commercial Strategy – Leveraging LUMEVOQ® Trial Centers to Build Network of LHON Centers of Excellence



- LHON experts mapped in both major and smaller markets
- Progressively build the LHON clinical network working with LHON experts
  - Recognize varying levels of LHON expertise and patient mobilization across markets
  - Balance patient reach with logistical complexity
- LHON expert- and LHON patient-centric commercial and medical teams executing focused local activities
  - Foster existing relationship with centers and LHON experts
  - Broaden LHON expert network locally and internationally
  - Manage patient and caregiver experience along the patient journey

# European Reimbursement Strategy – Short Term Revenues Generation Expected in H1 2022

		Commercial Launch (L) Q1 2022	L + 12 Months	L + 24 Months
3 Largest EU countries to generate revenues from H1 2022		Free pricing upon approval; benefit assessment; price negotiations	Negotiated price after 12 months; price influence on other markets	
		Free pricing upon approval; cost-effectiveness evaluation	Negotiated price after ~12-18 months; no influence from other markets	
		ATU price during P&R negotiations; clinical assessment; pricing agreement	Negotiated price after ~18 months; subject to reference pricing	
<b>Reimbursement</b> <ul style="list-style-type: none"> <li>• Compelling value communication</li> <li>• Robust post-launch Real World Data collection</li> <li>• Patient and clinician advocacy</li> <li>• Participation in pan-European access initiatives</li> </ul> 		~21 months of price negotiations* after approval	Negotiated price after ~21 months; subject to reference pricing	
		~24 months of price negotiations* after approval	Negotiated price after ~24 months; subject to reference pricing	

Note: Duration of negotiations depicted is based on industry benchmarks for recent rare disease launches; timings are illustrative

## Compassionate Use for LUMEVOQ® (GS010)

Seeking use of an investigational medication under circumstances a patient may not be able to participate in a clinical trial and before MA/BLA approval by regulatory authorities



- 18 individual patients Expanded Access INDs so far approved by the FDA for LUMEVOQ® (lenadogene nolparvovec)
- Additional individual patients Expanded Access INDs to be processed



ansm

- “ATU de Cohorte” or ATUc - Cohort Temporary Authorization for Use - for LUMEVOQ® granted by ANSM to GenSight on July 5, 2021
  - “ATU Nominative or ATUn” - named patient Temporary Authorization for Use - for LUMEVOQ® first authorized by ANSM to CHNO of the *Quinze-Vingts* in Paris in December 2019
- Bilateral injections priced at €700,000 per patient
  - €4.4M revenues generated in 2020
  - Increasing demand from physicians in 2021
  - Reimbursement warranted by the national Social Security up to €30M/year
- Named-Patient or Cohort Expanded Access Programs (EAP) in other European countries being set up to leverage LUMEVOQ® treatment for the benefit of patients accross Europe and beyond



# GS030

Second product candidate targeting photoreceptor degenerative diseases:

- Retinitis Pigmentosa (RP)
- Age-Related Macular Degeneration (AMD)

# Treating the 2 main degenerative diseases of photoreceptors that lead to blindness

## Retinitis Pigmentosa



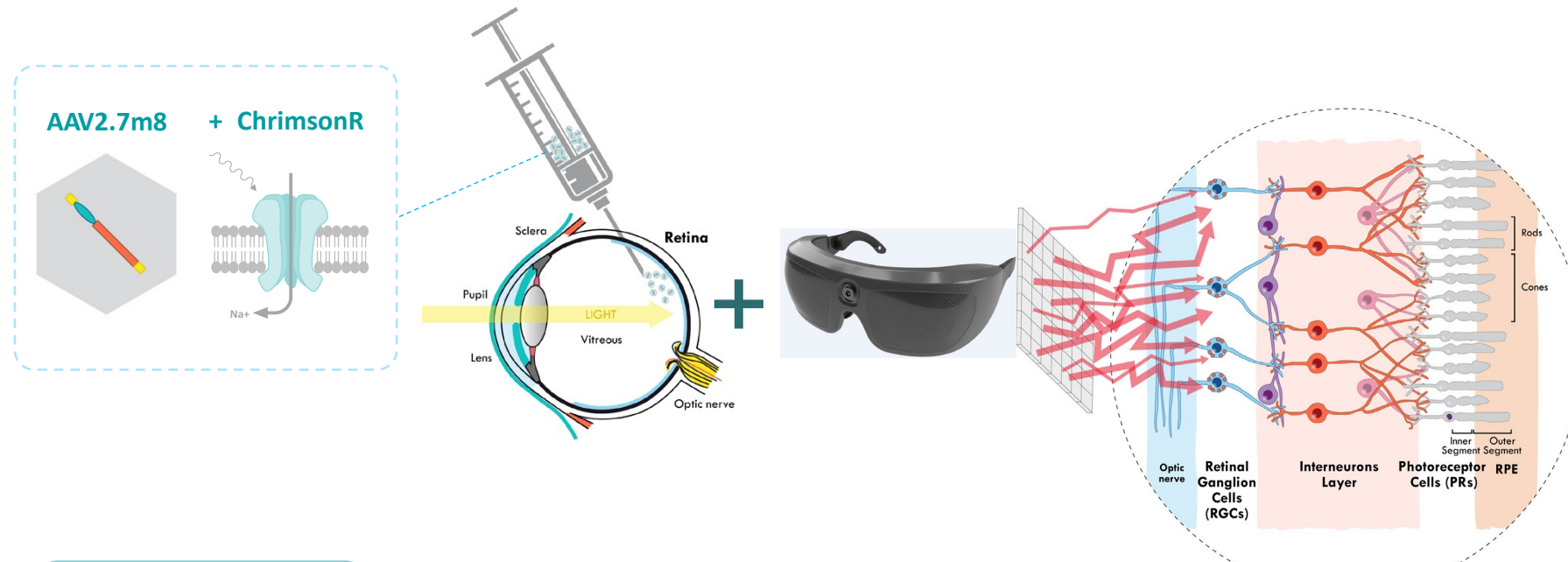
- Blinding genetic disease caused by mutations in over 100 different genes
- Sequential photoreceptor degeneration leads to slow & irreversible progression to blindness, usually at age 40-45
- 15-20,000 new patients each year in the US and EU

## Geographic Atrophy (GA) in AMD (Age-Related Macular Degeneration)



- Early (dry-form) AMD evolves with age into late AMD, one of whose forms is GA
- Dry-AMD affects 350-400,000 new patients a year
- Prevalence of GA increases with age, from 3.5% among 75-year-olds to 22% among those over 90
- Late AMD patients with GA account for 10-20% of blind patients in their age group

# GS030: using Gene Therapy to rejuvenate production of light-sensitive protein and restore vision



The product of research  
collaboration with



## Step 1

**Gene Therapy**  
transfer of the gene  
that encodes light-  
sensitive protein  
**Expression** in retinal  
ganglion cells (RGCs)

## Step 2

Stimulation with  
**optoelectronic  
device** to transform  
external light stimuli  
into signal that can  
activate the RGCs

## Step 3

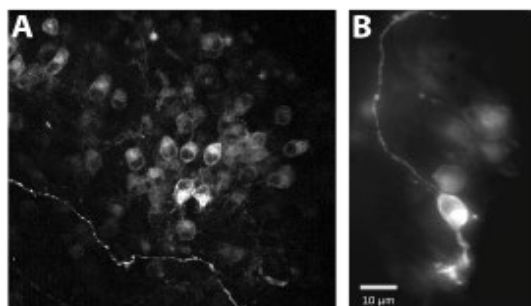
Retinal output sent  
to brain for image  
processing

# GS030 leads to functional vision restoration in monkey and rats

## Localization of light-sensitive protein in NHP retina

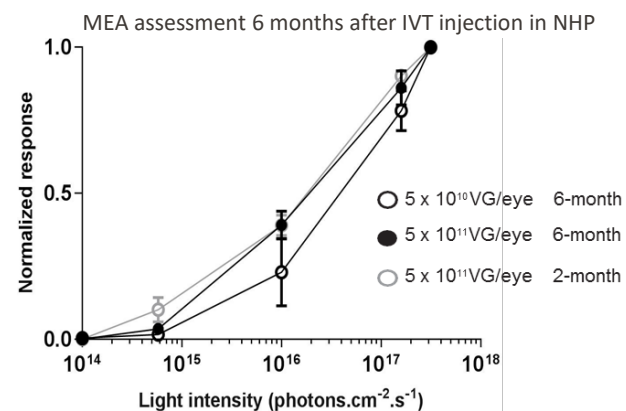
### Expression of ChrR-tdT in midget cells of monkey perifovea

*In vivo* in NHP assessment 6 months after IVT injection



## Dose-ranging response to firing relationship in NHP

### Active dose range : $5 \times 10^{10}$ and $5 \times 10^{11}$ VG/eye



### Recent publication

Optogenetic therapy: high spatiotemporal resolution and pattern discrimination compatible with vision restoration in non-human primates. Gauvain G. et al.

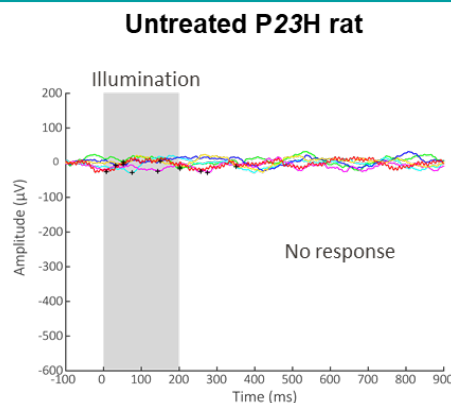
**Communications Biology, Feb. 2021**

<https://www.nature.com/articles/s42003-020-01594-w>

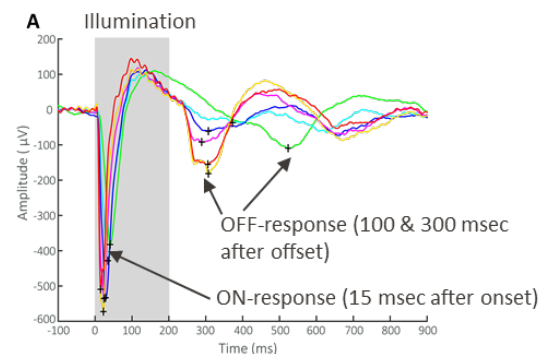
## Restoration of a functional vision in P23H rats

### Light-induced visual evoked cortical responses

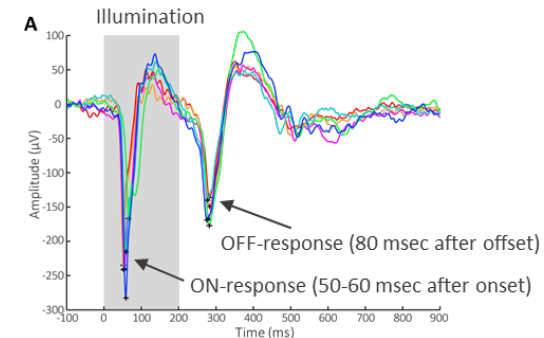
Full field 590 nm light from  
 $\sim 4.7 \times 10^{15}$  to  $1.1 \times 10^{17}$   
photons/cm<sup>2</sup>/sec



### GS030-treated P23H rat

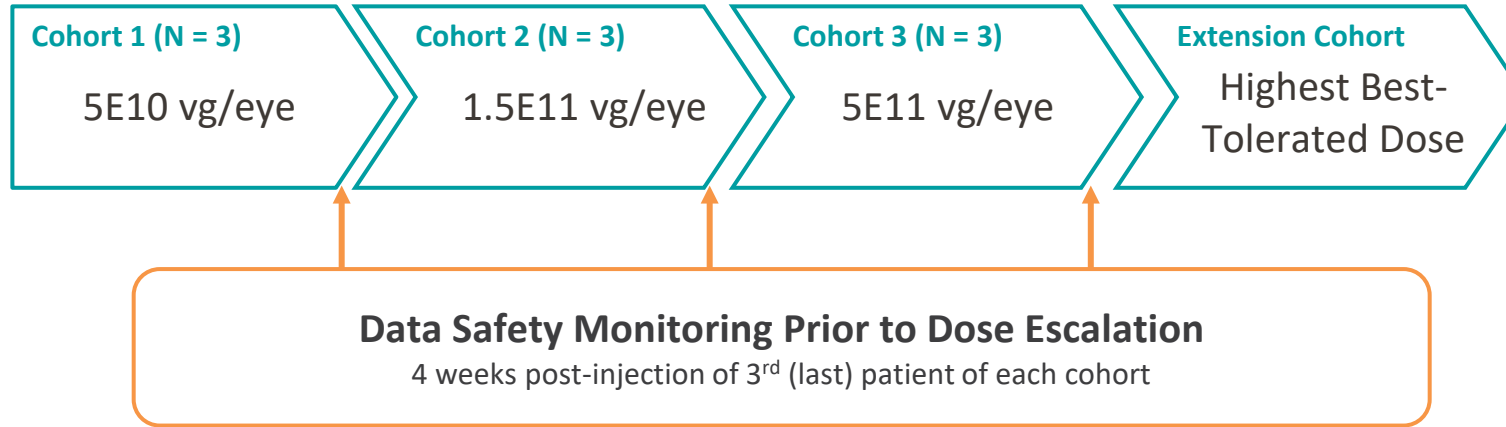


### Normal Long-Evans rat



# PIONEER Phase I/II clinical trial: A First-in-Man study

## Study design



- **First-in-man**, dose-escalation safety study, multi-center (France, UK, US)
- **Study population**: end-stage non-syndromic RP (vision < Counting Fingers)
- **Primary analysis**: Safety at 1 year
- Single intra-vitreal injection in the **worst affected** eye
- Decision to increase the dose taken by a DSMB

Extension Cohort with highest dose 5E11 vg/eye  
ongoing without any modification after DSMB#3 approval



## Recent publication

Partial recovery of visual function in a blind patient after optogenetic therapy.

Sahel J.A. et al., **Nature Medicine**, May 2021

<https://www.nature.com/articles/s41591-021-01351-4>



Video of the patient performing the tests  
available on [www.gensight-biologics.com](http://www.gensight-biologics.com).

Building high strategic value



# A company developing innovative and versatile technology platforms nearing commercialization and evolving in an area where value is increasingly being recognized by the market

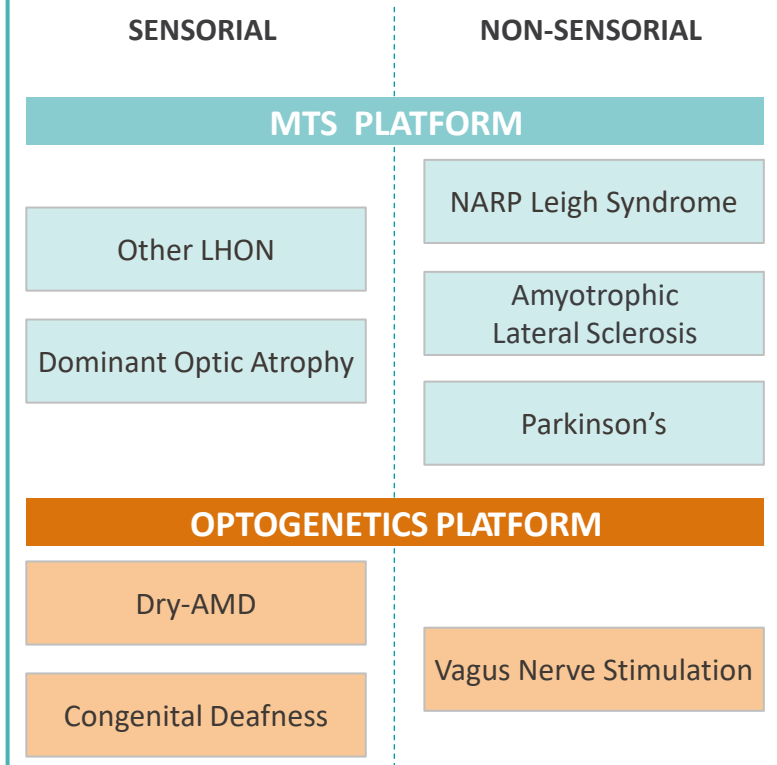
## GenSight at the forefront of Gene Therapy with potential product launch in 2021

- » **LUMEVOQ® in LHON-ND4**
  - Strong clinical data
  - Upcoming confirmatory Phase III trial
- » **Targets attractive market**
  - High unmet medical need
  - Virtually no competition
  - Well defined path to commercial success
- » **Proprietary MTS technology**
  - Broad range of mitochondrial diseases
- » **Rich news flow** in 2020 and 2021

## Gene Therapy increasingly attracts interest from investors and Large Pharma

- » **Viable therapeutic option** (already 3 approved therapies)
- » **Pricing reflective of significant therapeutic benefit**
- » **Large Pharma increasingly involved in the field**

## LUMEVOQ® and Beyond: Two platforms targeting large number of sensorial and non-sensorial diseases





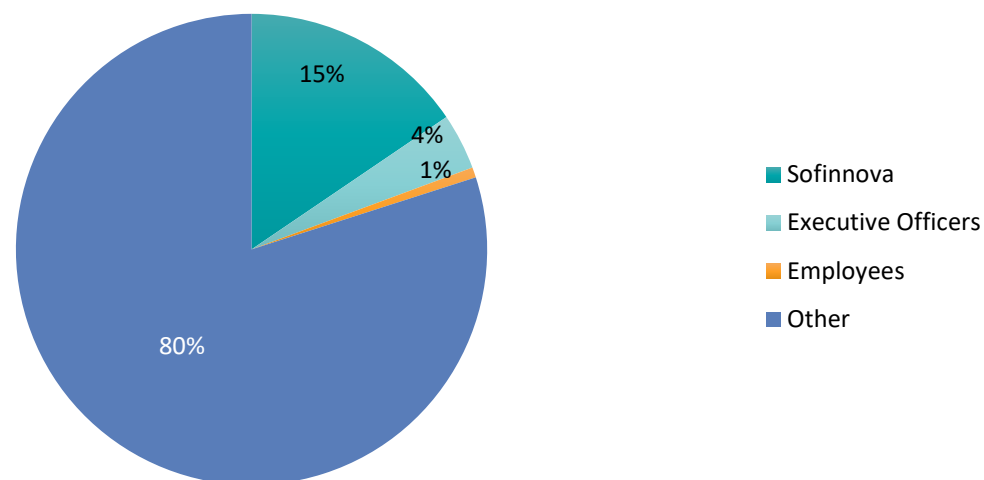
# GenSight Biologics in numbers

## Key financial information

Company Overview		
Market Cap*:	€ 423m	<b>Analyst Coverage</b>
Cash Position (June 30, 2021):	€ 54.3 m	• Chardan: Gbola Amusa (US)
Outstanding Shares:	46.0m	• Bryan Garnier: Dylan van Haaften (FR)
Latest Amount Raised (March 2021):	€ 30m	• Oddo BHF: Sébastien Malafosse (FR)
Raised to date	€ 197m	
IPO Date	July 2016	

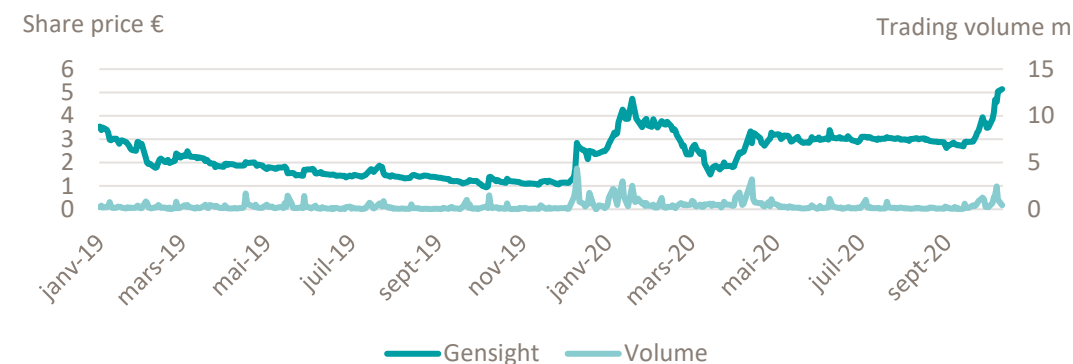
\*As of May 3, 2021

## Shareholder structure



As of May 2021

## Share price evolution and trading volume



## Corporate calendar

	Date
2020 Full-Year Financial Update and Statements	March 10, 2021
2021 1Q Cash Position	April 20, 2021
Annual General Meeting	April 29, 2021
2021 First-Half Financial Update and Statements	July 29, 2021
2021 3Q Cash Position	November 10, 2021
2021 4Q Cash Position	January 18, 2022

# Appendix



# RESCUE & REVERSE Phase III trials with unilateral injection demonstrated unprecedented improvement

Different patient inclusion criteria

Same design

Visual recovery at Week 96 and vs natural history

## REVERSE



- Onset of disease **6 months to ≤ 1 year**
- 37 patients enrolled

- Double-masked, multi-center
- One eye randomized to GS010; other eye received sham injection

Group 1



GS010 in right eye  
SHAM in left eye

Group 2

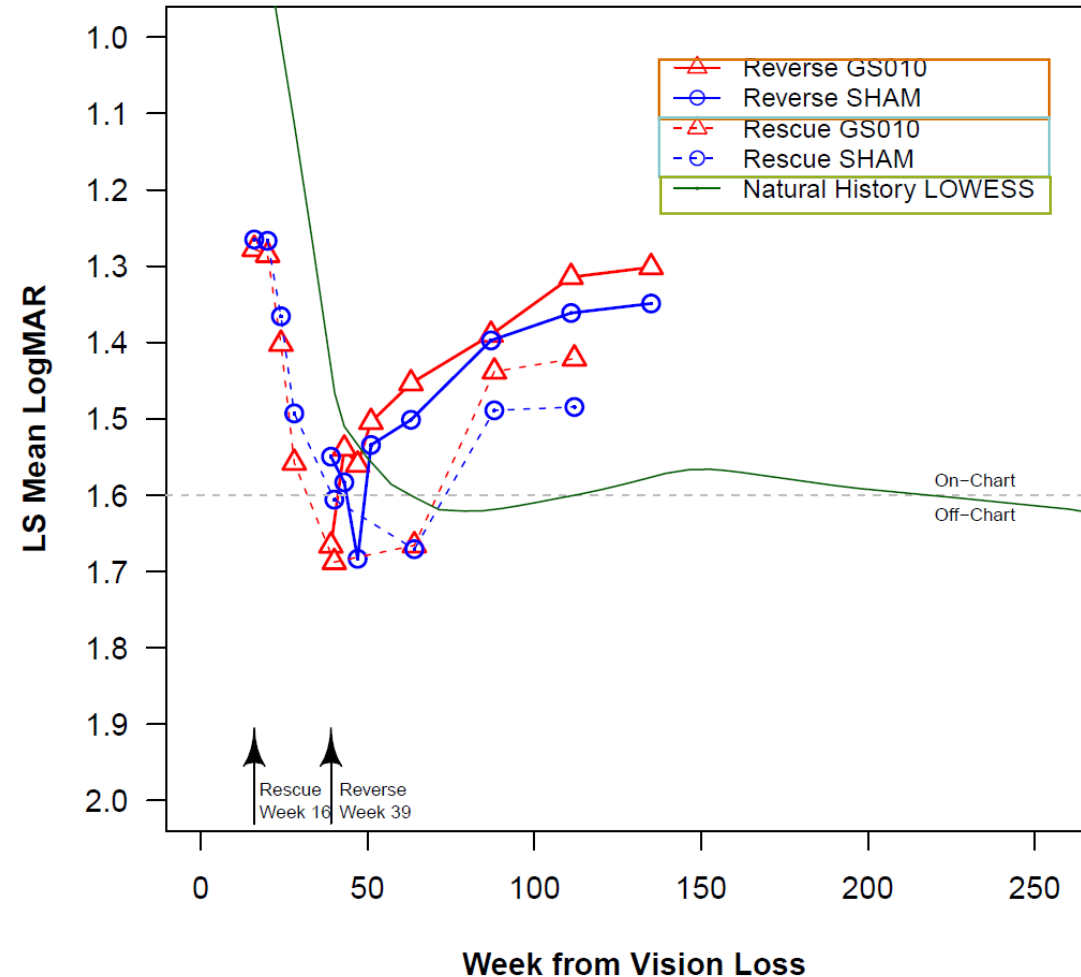


SHAM in right eye  
GS010 in left eye

## RESCUE



- Onset of disease **≤ 6 months**
- 39 patients enrolled



+28 ETDRS Letters vs nadir



+26 ETDRS Letters vs nadir

**REVERSE and RESCUE: Final Results**  
75 ND4 Subjects ≥ 15 years old – Over 2 year-follow-up



Retrospective Natural History

**REALITY: Final Results**  
23\* ND4 Subjects ≥ 15 years old – Over 5 year-follow-up

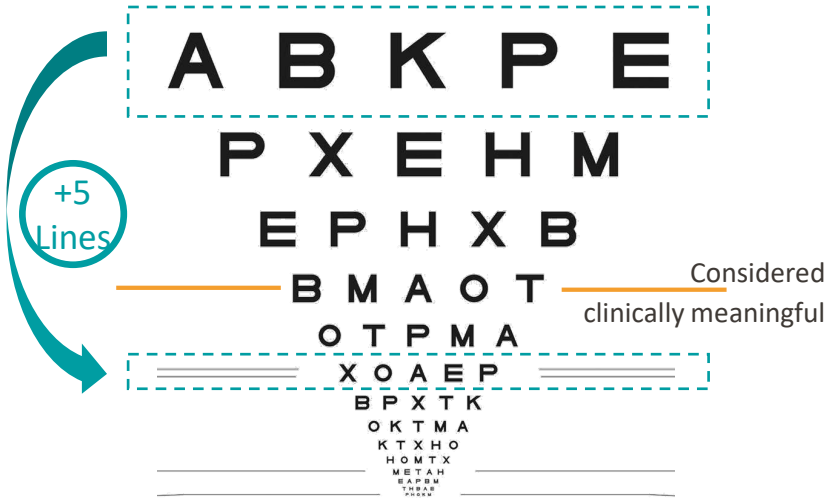
\*: Out of which, 15 had been treated with idebenone, the majority within 12 months of their vision loss

# Visual Acuity: Improvement of BCVA from NADIR

Visual Acuity deteriorates to a low point before recovering significantly in both eyes



Change from NADIR in ETDRS letter equivalents			Change from NADIR in ETDRS letter equivalents		
Week 96			Week 96		
	n	Mean (SD)		n	Mean (SD)
All-GS010 eyes	37	+28.3 (22.5)	All-GS010 eyes	34	+26.3 (23.9)
All-sham eyes	37	+24.5 (24.0)	All-sham eyes	34	+22.8 (24.2)



NADIR was defined as the **worst** BCVA from baseline to Week 96  
Mean change from nadir was calculated using observed values (no data imputation)


Unparalleled clinical benefit demonstrated with LUMEVOQ® (GS010) in LHON in two Phase III studies:  
+28/+26 ETDRS letters (i.e. over 5 lines on visual scale) improvement vs nadir


# 3-year long-term follow-up: sustained efficacy and safety

Change from NADIR in ETDRS letter equivalents			
	n	Year 2 post-injection Mean (SD)	Year 3 post-injection Mean (SD)
All-GS010 eyes	61	+18.8 (15.3)	+20.5 (18.3)
All-sham eyes	61	+17.3 (14.6)	+19.4 (18.5)

The CLIN06 sample consists of the RESCUE and REVERSE participants who accepted to be followed in the CLIN06 study

NADIR was defined as the **worst BCVA** from baseline to Week 96 and 144  
Mean change from nadir was calculated using observed values (no data imputation)

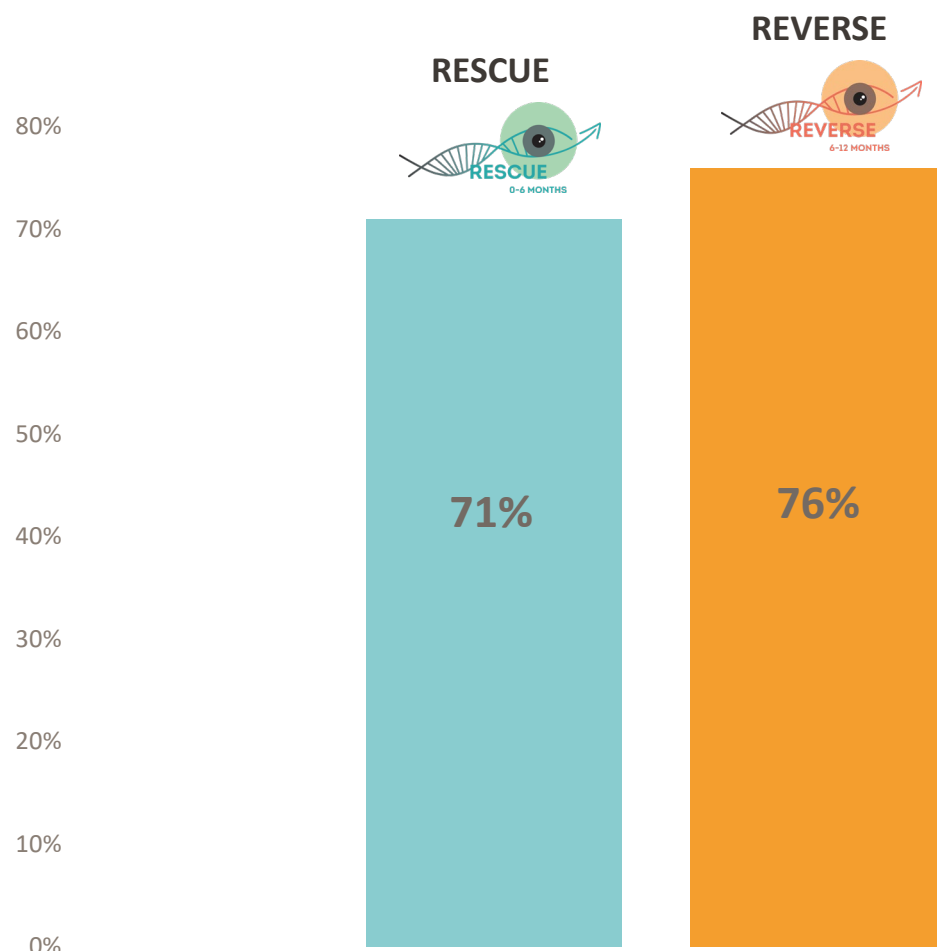
  
n=37

  
n=34

**CLIN06 – long-term follow-up study**

n=31                      n=30

# REVERSE and RESCUE demonstrate that over 70% of patients benefit from treatment



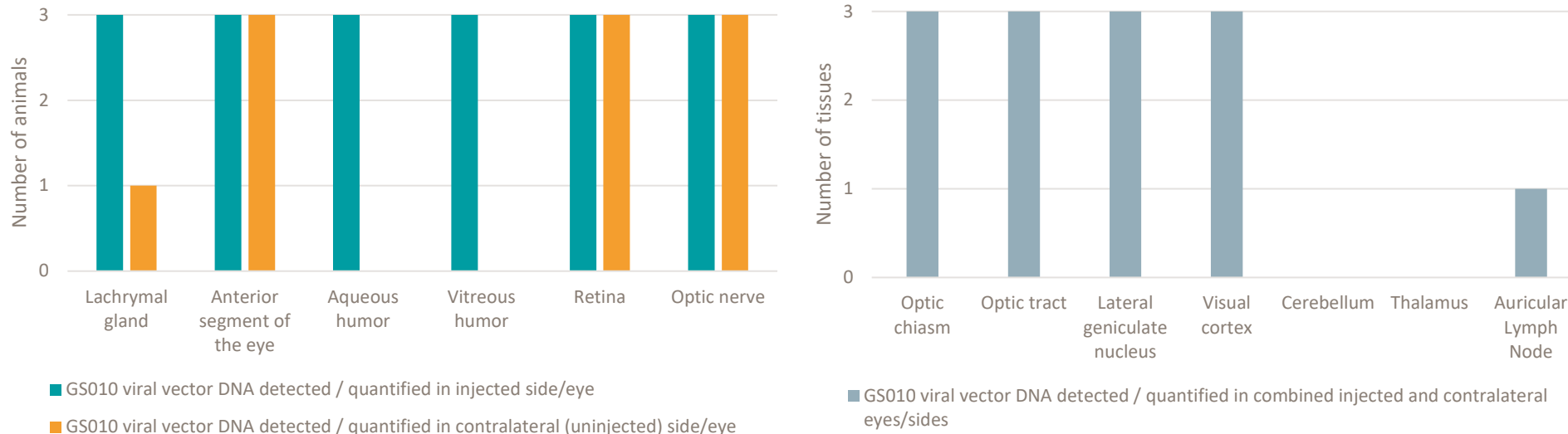
**76% of REVERSE subjects** achieved at least 15 letters improvement vs nadir in one or two eyes

**71% of RESCUE subjects** achieved at least 15 letters improvement vs nadir in one or two eyes

# GS010 (LUMEVOQ®) viral vector DNA detection in uninjected eye of monkeys supports bilateral effect in REVERSE and RESCUE Phase III trials

Viral vector DNA detected in uninjected eye → potential mechanism for bilateral effect in REVERSE and RESCUE

Presence of GS010 DNA in the visual and cerebral systems of test monkey at 3 months after GS010 injection



The bar graph indicates the number of animals (of three) in which rAAV2/2-ND4 (GS010) DNA was present above the limit of detection (15.6 copies/μg of DNA).

Source: Yu-Wai-Man P. et al., Sci Transl Med. Dec. 2020

*“The presence of viral vector DNA in the optic chiasm and optic nerve of the contralateral uninjected eye points towards a possible diffusion pathway.”*

**Dr. Patrick Yu-Wai-Man**, Senior Lecturer & Honorary Consultant Ophthalmologist at the University of Cambridge, Moorfields Eye Hospital, and the UCL Institute of Ophthalmology, London, UK

Notes: One control monkey was injected in one eye with saline solution. Three test monkeys were injected with GS010 in one eye using dose allometrically equivalent to that used in REVERSE and RESCUE. Tissue samples were taken at 3 months after injection and tested using a protocol that specifically targeted the CMV promoter of the GS010 DNA. The sensitivity, specificity and accuracy of the test were validated in a dedicated study.

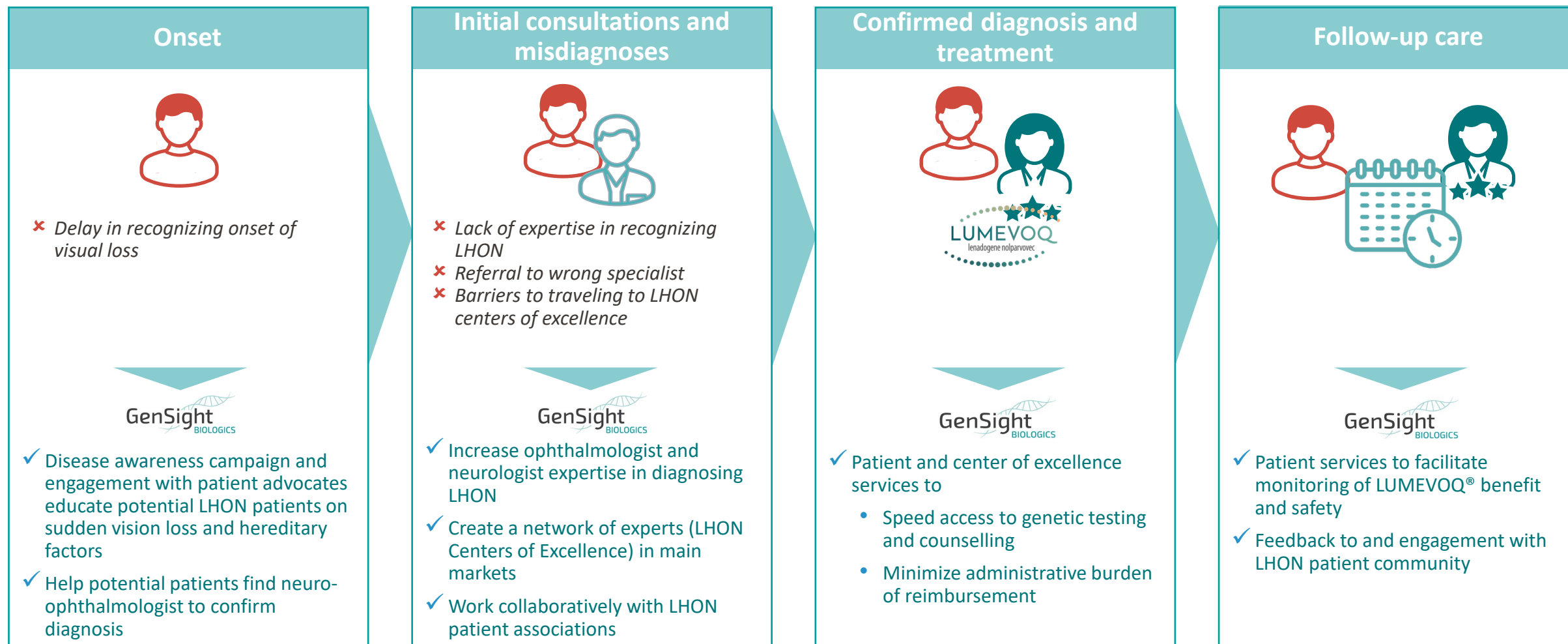
- Three test monkeys injected in one eye using dose equivalent of treatment in REVERSE and RESCUE trials
- Highly sensitive validated test for presence of GS010 DNA used on tissue samples from primates in study

**Key finding:**

- GS010 viral vector DNA was detected/quantified in many tissue samples from contralateral (uninjected) eye



# European Commercial Strategy - Facilitate and Speed Up Patient Access to LUMEVOQ®



# LUMEVOQ®: From lab to hospital (1/3)



The optimized allotopic expression of ND1 or ND4 genes restores respiratory chain complex I activity in fibroblasts harboring mutations in these genes

Bonnet C. et al., Biochim Biophys Acta., May 2008



Optimized allotopic expression of the human mitochondrial ND4 prevents blindness in a rat model of mitochondrial dysfunction

Ellouze S. et al., Am J Hum Genet., Sep. 2008

Nuclear expression of mitochondrial ND4 leads to the protein assembling in complex I and prevents optic atrophy and visual loss

Cwerman-Thibault H. et al., Mol Ther Methods Clin Dev., Feb. 2015



Safety of rAAV2/2-ND4 Gene Therapy for Leber Hereditary Optic Neuropathy

Vignal C. et al., Ophthalmology, Feb. 2018

Immune Response and Intraocular Inflammation in Patients With Leber Hereditary Optic Neuropathy Treated With Intravitreal Injection of Recombinant Adeno-Associated Virus 2 Carrying the ND4 Gene: A Secondary Analysis of a Phase 1/2 Clinical Trial

Bouquet C. et al., JAMA Ophthalmol., April 2019



Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy

Yu-Wai-Man P. et al., Sci Transl Med. Dec. 2020

# LUMEVOQ®: From lab to hospital (2/3)



Efficacy and safety of intravitreal gene therapy for Leber hereditary optic neuropathy treated within 6 months of disease onset

Newman N.J. et al., Ophthalmology, Jan. 2021



Safety of intravitreal gene therapy for treatment of subjects with Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial ND4 gene – The REVEAL study

Vignal-Clermont C. et al. BioDrugs, Feb. 2021



Natural History of Patients with Leber Hereditary Optic Neuropathy – Results from the REALITY Study

Yu-Wai-Man P. et al., Eye, April 2021



Intravitreal Gene Therapy vs. Natural History in Patients with Leber Hereditary Optic Neuropathy Carrying the m.11778G>A ND4 Mutation: Systematic Review and Indirect Comparison

Newman N.J., et al., Front. Neurol., May 2021



Long-Term Follow-Up After Unilateral Intravitreal Gene Therapy for Leber Hereditary Optic Neuropathy: The RESTORE Study

Biousse V. et al., J. Neuro-Ophthalmol., Sep. 2021



Cross-Sectional Analysis of Baseline Visual Parameters in Subjects Recruited into the RESCUE and REVERSE ND4-LHON Gene Therapy Studies

Moster M. L. et al., J. Neuro-Ophthalmol., Sep. 2021

# LUMEVOQ®: From lab to hospital (3/3)



Gene Therapies for the Treatment of Leber Hereditary Optic Neuropathy

Sahel J.A. et al., Int. Ophthalmol. Clin., Oct. 2021

## Recent scientific publications related to LHON

Visual Outcomes in Leber Hereditary Optic Neuropathy Patients With the m.11778G.A (MTND4) Mitochondrial DNA Mutation

Newman N.J., et al., J. Neuro-Ophthalmol Dec. 2020 - Volume 40 - Issue 4 - p 547-557