GenSight BIOLOGICS

Corporate Presentation

May 2019

A LEADING GENE THERAPY BIOTECHNOLOGY COMPANY

GENSIGHT-BIOLOGICS.COM

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GenSight BIOLOGICS

Corporate Overview

Clinical-stage gene therapy company

- Focused on severe retinal degenerative pathologies leading to blindness as well as CNS diseases
- Well positioned to advance disruptive gene therapy technologies in ophthalmology to commercialization

Two disruptive technology platforms

- Mitochondrial targeting sequence (MTS)
- Optogenetics

Lead projects target:

- GS010 - Leber Hereditary Optic Neuropathy (Phase III)
- GS030 - Retinitis pigmentosa and dry-AMD (Phase I/II)

Listed on Euronext Paris (SIGHT)

- Established in 2012, IPO in July 2016 (EUR45m)
- GenSight Biologics Inc incorporated in the US in May 2017

GenSight BIOLOGICS

Executive Team

Bernard Gilly
Chief Executive Officer

PIXIUM VISION (Since 2011)
Chairman of the Board, Founder

FOVEA PHARMA (2005-2009)
Chairman & CEO – sold to Sanofi

SOFINNOVA PARTNERS (2000-2005)
Managing Partner

TRANSGENE (1992-2000)
Chairman & CEO

Ph.D. in biology and bio-economics

Thomas Gidoin
Chief Financial Officer

DBV TECHNOLOGIES (2012-2015)
VP of Finance

IPSEN (2008-2011)
UK Operations Controller (London)
Senior Financial Analyst (Paris)

ERNST & YOUNG (2007-2008)
Auditor

Barrett Katz
Chief Medical Officer

MONTEFIORE MED CENTER & A. EINSTEIN COLLEGE OF MEDICINE, NY, USA (2011-2017)
Prof. of Ophthalmology, Neurology and Neurosurgery

DANUBE PHARMA (2009-2011)
CEO

FOVEA PHARMA (2007-2009)
CMO

EYETECH (2005-2007)
VP of Medical Affairs and Strategy

MD, Board-certified ophthalmologist & neurologist

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Our target: degenerative retinal diseases with underlying genetic causes

LEBER HEREDITARY OPTIC NEUROPATHY (LHON)

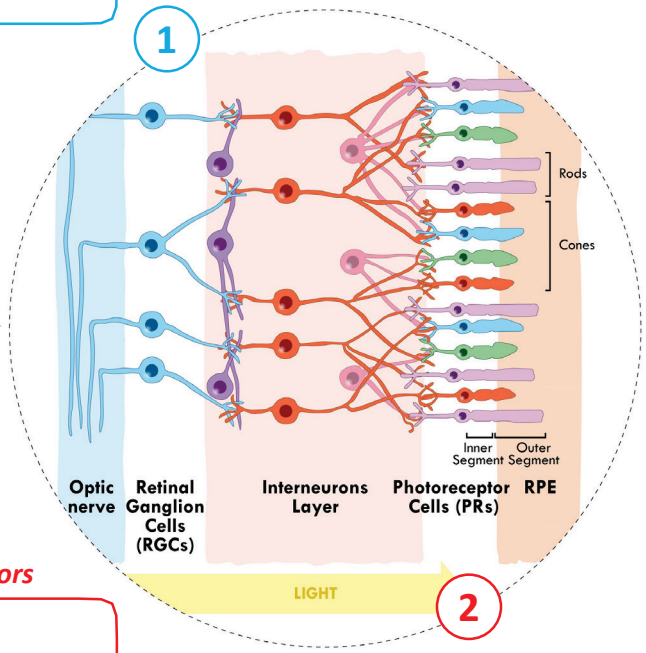
1. Degeneration of RGCs

Genetic mutations
Aging

2. Degeneration of photoreceptors

RETINITIS PIGMENTOSA (RP)

GEOGRAPHIC ATROPHY
(Late stage form of Age-Related Macular Degeneration - AMD)



✓ **Unmet need: high**

- Inexorable progression to blindness for most patients
- No approved treatments*

✓ **The eye: an ideal laboratory**

- Immune-privileged, closed system
- Intravitreal injections to introduce of genetic material close to target cells
- Slow turnover of retinal cells support long-term expression of transduced genes

✓ **AAV: proven vector for gene therapy**

- Proven safety and proof of effect in humans
- Efficient transduction of retinal cells
- No need to screen patients for Nab before treatment
- Validated manufacturing process

Source: Company
*Except for exceptional circumstances for idebenone in Europe

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Pipeline: solid and advanced product portfolio in ophthalmic gene therapy

Technology	Product Candidate	Indication	Research	Preclinical	Phase I/II	Phase III	Registration	Next Expected Events
MTS platform	**GS010** (FDA & EMA Orphan Drug Designation)	**LHON ND4**	● →	→	→	→		**REVERSE**: Phase III top-line data reported in Apr (48w) & Oct (72w) 2018 and in May 2019 (96w). **RESCUE**: Phase III top-line data reported in Feb (48w) and Apr (72w) 2019. 96w expected in Sep 2019. **REFLECT***: Phase III recruitment ongoing, top-line data expected in Q2 2020
	GS011	**LHON ND1**	● →					Initiate preclinical studies following GS010 Phase III clinical data
	Undisclosed Mitochondrial Target	Undisclosed	● →					
Optogenetics	**GS030** (FDA & EMA Orphan Drug Designation)	**RP**	● →	→	→			**PIONEER**: First cohort injected in ongoing Phase I/II clinical trial. Report interim data one year after last subject treated
	GS030	**Dry AMD & Geographic Atrophy**	● →					

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

Lead candidate, GS010, is expected to be less than 12 months away from MAA submission in Europe

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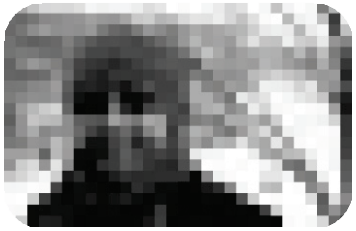
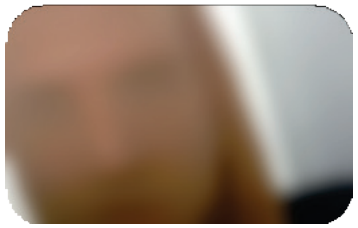
GS010

Fully enrolled Phase III trials for our lead product candidate dedicated to Leber Hereditary Optic Neuropathy (LHON)

GS010 aim: treat LHON, the most common mitochondrial disease causing bilateral blindness in the prime of life





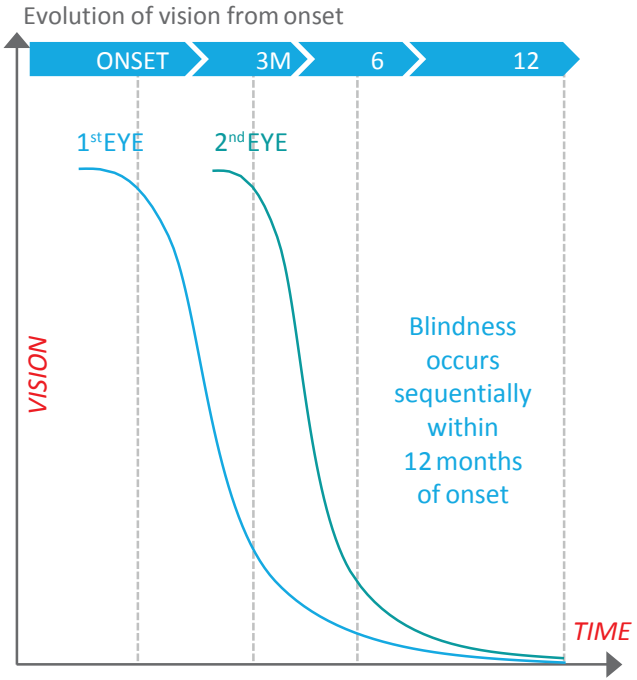


Image source: illustrated from Newamn NJ et al., Am J Ophthalmom. 141(6), 1061-1067,2006

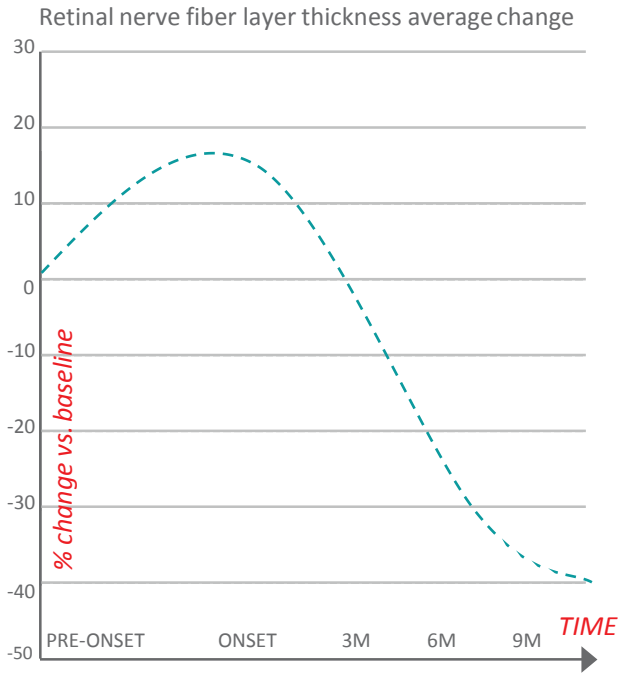


Image source: illustrated from Barboni et al Natural History of Leber's Hereditary Optic Neuropathy: An OCT Study

Incidence	0.15/100,000
Prevalence	1/31k-40k
Blindness	15-35y

- **Orphan maternally inherited mitochondrial disease**
- **Painless sudden loss of central vision** in the 1st eye with 2nd eye sequentially impaired: **symmetric disease with poor visual recovery**
- **Thinning of the Ganglion Cell Layer** occurs after the onset of vision loss and stabilizes at approximately 6 months
- **97%** of patients have bilateral involvement < 1 year / 25% of cases are simultaneous
- **Targets ND4** which accounts for ~75% of LHON in North America & Europe

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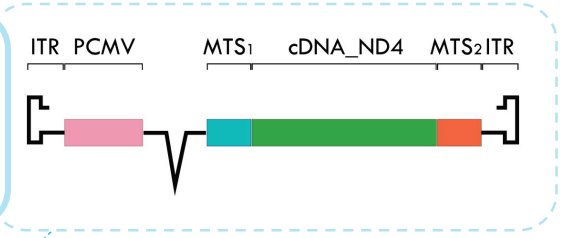
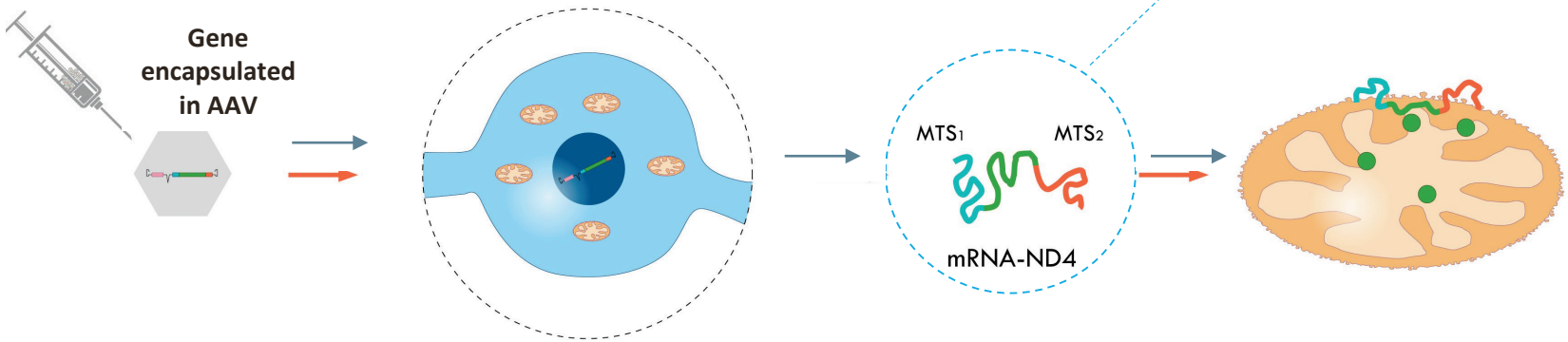
Solution: Gene therapy to produce working mRNA, with ***MTS* technology*** to shuttle mRNA directly to affected mitochondria

MTS in action for GS010:

The product of research collaboration with Inserm





Step 1

Retinal cell transduced with vector containing wild-type mitochondrial gene

Step 2

Wild-type mitochondrial gene transcribed in the nucleus

Step 3

Wild-type mRNA **delivered by MTS directly** to polysomes located at the mitochondrial surface, where protein synthesis occurs

Step 4

Finally, the wild-type mitochondrial protein is translocated inside the mitochondrion, where it **restores energy production**

Gene therapy

*MTS**

*MTS = mitochondrial targeting sequence

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RESCUE & REVERSE Phase III trials

Time-based strategy to assess GS010 efficacy

Different patient inclusion criteria → **Same design** → **Same endpoints at Week 48**

REVERSE

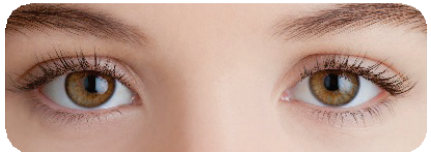
- Onset of disease **6 months to ≤ 1 year**
- 37 patients enrolled
- Fully enrolled Feb 2017

RESCUE

- Onset of disease **≤ 6 months**
- 39 patients enrolled
- Fully enrolled July 2017

- 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

Primary

- Mean difference change from baseline, ETDRS letters, drug treated eyes vs. sham treated eyes (LogMAR used for statistical analysis) at Week 48

Secondary

- SD-OCT, visual field, color and contrast vision
- Responders analysis:
  - Gain from baseline of 15 or more ETDRS letters
  - Snellen acuity > 20/200
- Treated vs. sham eyes' BCVA for best-seeing and worst-seeing eyes
- Quality of life assessments

Source: Company

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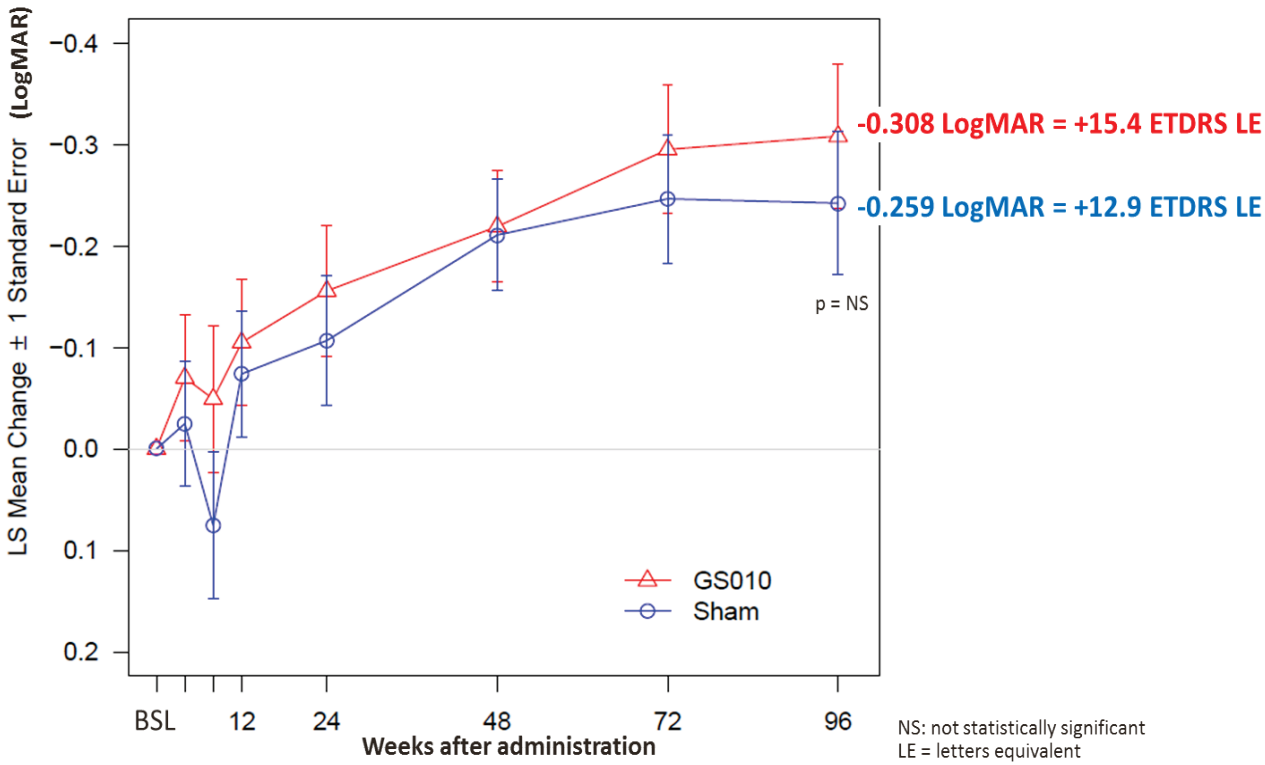
Visual Acuity: REVERSE 96-week

Visual Acuity bilaterally improved by +15 and +13 ETDRS letters equivalent from baseline to Week 96 in GS010- and sham-treated eyes, respectively, sustaining the gain at Week 72

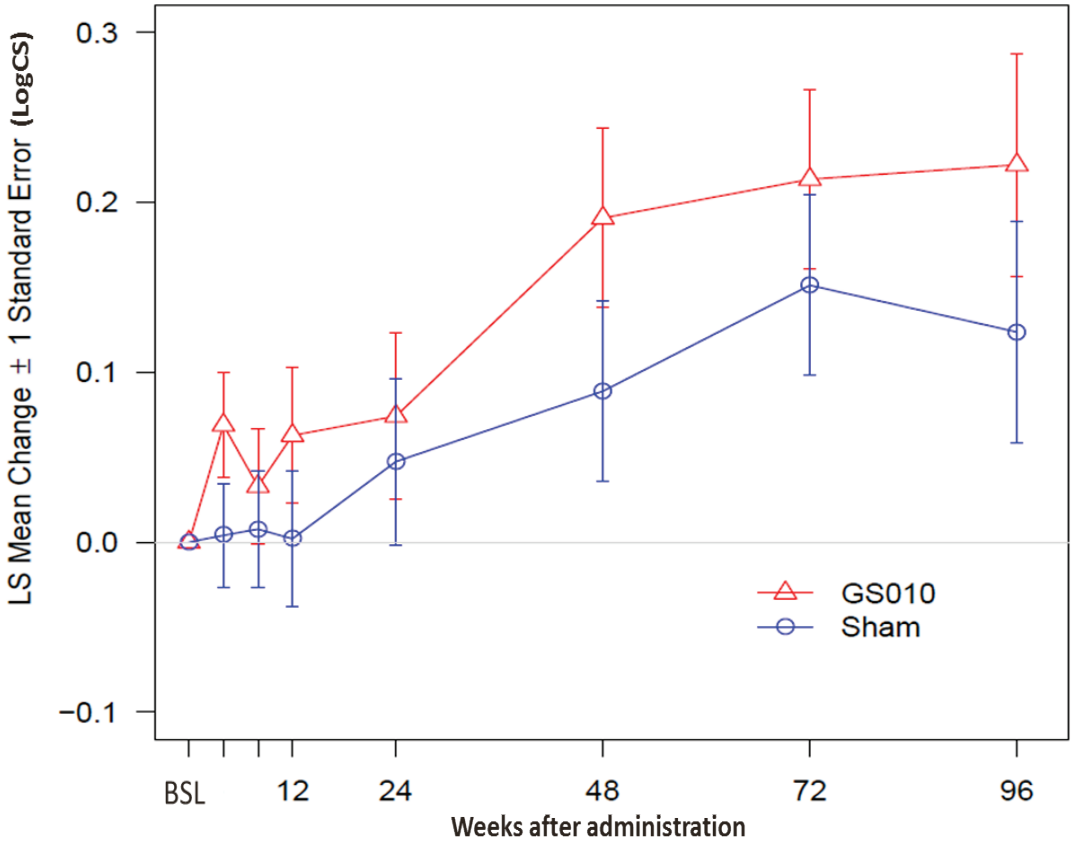


NS: not statistically significant
LE = letters equivalent

Mean visual acuity (BCVA) among GS010-treated eyes and sham-treated eyes evolved with similar trajectories, worsening to a post-treatment low point, or nadir, before recovering at Week 96 by +28 and +23 ETDRS letters equivalent, respectively

Contrast Sensitivity: REVERSE 96-week

Like BCVA, contrast sensitivity (Pelli-Robson) showed a bilateral trend, improving from baseline to Week 96 in both GS010-treated and sham eyes



Mean contrast sensitivity for GS010-treated eyes showed a more robust improvement versus baseline over the course of the trial comparing to sham-treated eyes

Responder Analysis: REVERSE 96-week

- **65% of GS010-treated and 46% of sham-treated eyes** achieved a clinically meaningful BCVA improvement from baseline (-0.2 LogMAR or +10 ETDRS letters) at Week 96
  (p = 0.0348, statistically significant difference)

- Based on a generalized estimating estimation (GEE) model, GS010-treated eyes were 3.6 times more likely to be above the legal threshold of blindness of 20/200 than sham-treated eyes
  (p = 0.0032, statistically significant difference)

"It is encouraging that GS010-treated eyes were nearly four times more likely to achieve vision better than 20/200 compared with sham eyes. The next step, which is to analyze individual longitudinal data on the visual parameters for each subject recruited into REVERSE, should further clarify the therapeutic benefit of GS010 in 11778-ND4 LHON."

Dr. Patrick Yu-Wai-Man

Senior Lecturer and Honorary Consultant Ophthalmologist at the University of Cambridge; Moorfields Eye Hospital, London; and the UCL Institute of Ophthalmology, London, UK

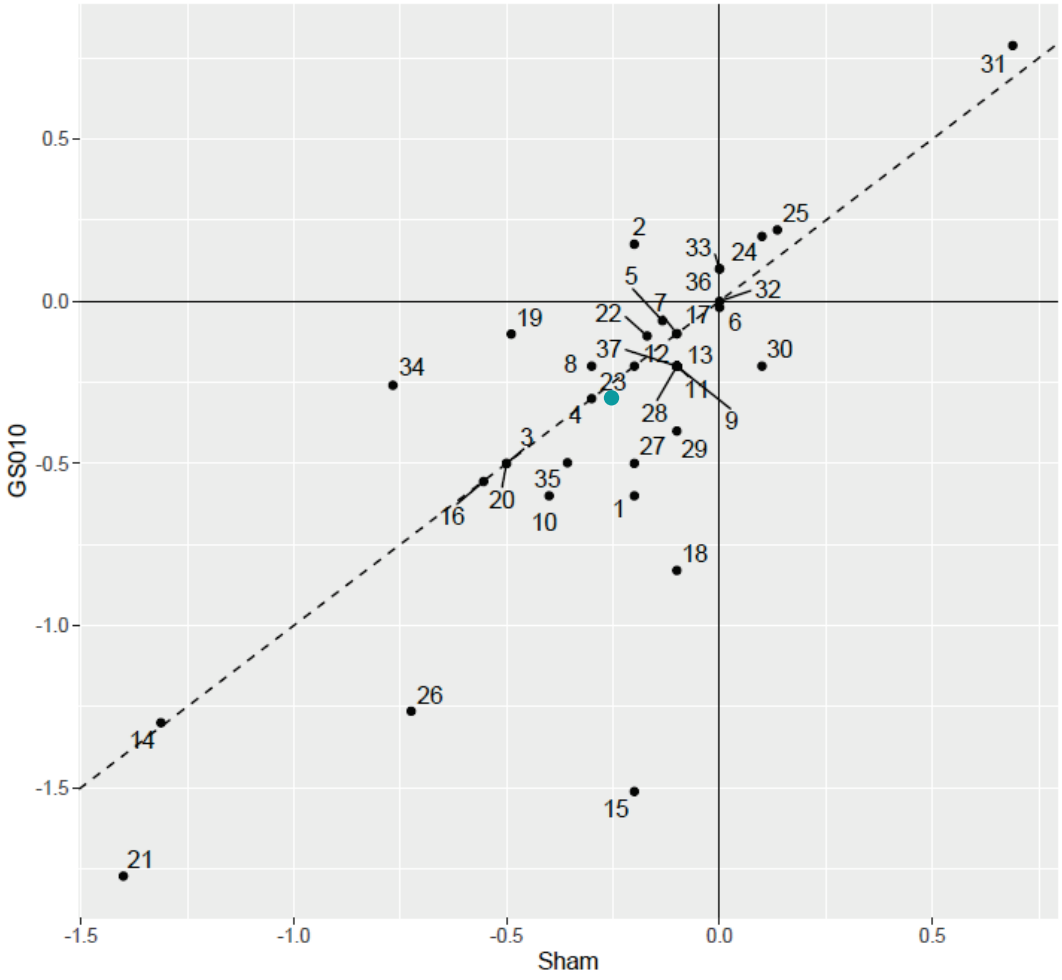
Bilateral improvements in visual function, though more prominent in GS010-treated eyes

Responder Analysis: Subjects Mapping in REVERSE at 96 weeks

Visual Acuity Change of Sham eyes was correlated with that of GS010 eyes in most REVERSE subjects
Subjects are well concentrated around the mean

REVERSE – Scatterplot of Change from Baseline at Week 96

Pearson Corr Coeff = 0.776; p – 1.677^{e}-08 / Spearman Corr Coeff = 0.727; p = 3.492^{e}-07



- **LS Mean in LogMAR (SE)**
  GS010 = -0.294 (0.063)
  Sham = -0.246 (0.063)

Natural History: REVERSE 96-week

Comparison to natural history based on a study by Santhera[1]

- In a **natural history study** conducted by Santhera[1], **15% of subjects** with the ND4 (*11778A*) mutation achieved the following definition of "clinically relevant recovery" (CRR) from baseline in at least one eye:
  - » Improved by at least 10 ETDRS letters from their on-chart visual acuity, or
  - » Improved from an off-chart level of visual acuity to being able to read at least 5 ETDRS letters (on-chart)

By comparison …

- **68% of REVERSE subjects** achieved this definition of CRR at Week 96, with GS010-treated eyes significantly more likely to achieve this than sham-treated eyes (62% vs. 43%, p = 0.0348, statistically significant difference).

"The data show that both the treated and the sham eye improved in both high and low contrast, defying the accepted natural history of this disease and improving upon it, based upon the clinical experiences of generations of neuro-ophthalmologists."

Dr. Robert C. Sergott

Director, Wills Eye Hospital, Neuro-Ophthalmology and Director, William H. Annesley, Jr, EyeBrain Center, Thomas Jefferson University, Philadelphia, PA

REVERSE subjects experienced a significantly higher rate of "clinically relevant recovery" than natural history

(1) Magda et al (2019), "Natural History of Leber's Hereditary Optic Neuropathy (LHON): Findings from a Large Patient Cohort", Poster presented at NANOS March 16-21, 2019; Poster Session II: Scientific Advancements; Poster: 163

Retinal Anatomy: REVERSE 96-week

Anatomic outcomes

Structural metrics indicate that GS010-treated eyes maintained the stability achieved in previous readouts in ganglion cell volume

"The behavior of the untreated eye must make us re-examine what we thought we knew as possibly dogma and be open to the idea that gene therapy delivered into one eye may be able to access the contralateral eye."

Dr. Robert C. Sergott

Director, Wills Eye Hospital, Neuro-Ophthalmology, and Director, William H. Annesley, Jr, EyeBrain Center, Thomas Jefferson University, Philadelphia, PA

Difference between GS010-treated and sham eyes not statistically significant at Week 96, but more prominent in earlier readouts

Quality of Life: REVERSE 96-week

Sustained Quality of Life improvement

- Composite score and relevant sub-scores in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) showed sustained improvements versus baseline at Week 48, Week 72 and Week 96
- Magnitudes of mean score improvement observed with GS010 correlate with clinically meaningful improvements in best-corrected visual acuity (BCVA)

NEI VFQ-25 Results from REVERSE

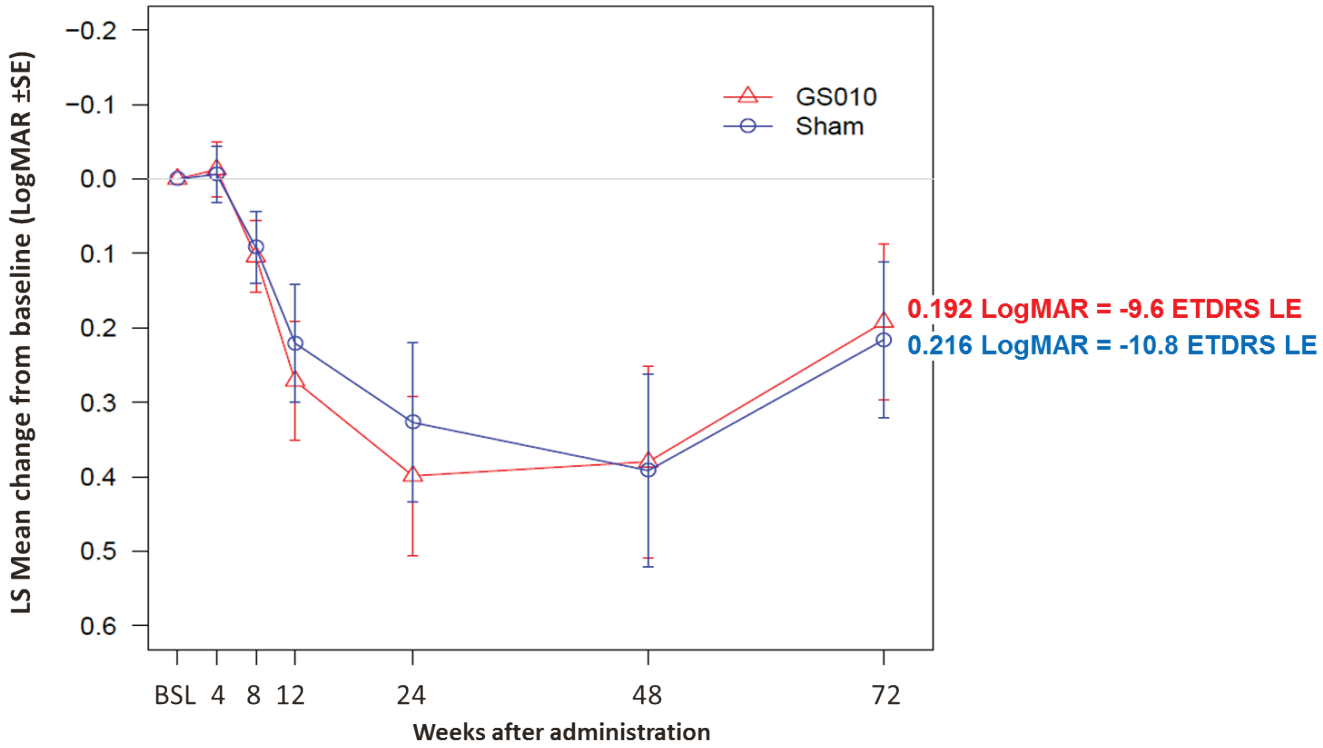
Mean change from baseline (absolute score and percent)

	Composite Score**	Near Activities	Distance Activities	Dependency	Role Difficulties	General Vision	Mental Health
Week 48	+7.2 *+23.2%*	+10.4 *+65.1%*	+9.6 *+49.8%*	+12.4 *+100.6%*	+14.5 *+65.0%*	+10.3 *+50.9%*	+11.2 *+81.9%*
Week 72	+8.1 *+25.2%*	+9.5 *+58.1%*	+8.2 *+42.5%*	+18.9 *+130.2%*	+15.2 *+70.9%*	+11.9 *+54.1%*	+15.2 *+105.6%*
Week 96	+9.5 *+28.8%*	+13.3 *+78.1%*	+10.7 *+47.4%*	+18.5 *130.2%*	+15.9 *+78.9%*	+6.5 *+32.4%*	+16.1 *+108.2%*
Clinically relevant difference*	+3.90 to +4.34	+4.67 to +6.06	+5.15 to +5.38	+4.72 to +4.98	+3.31 to +4.70	+4.38 to +4.82	+4.70 to +4.88

*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.

Visual Acuity: RESCUE 72-week

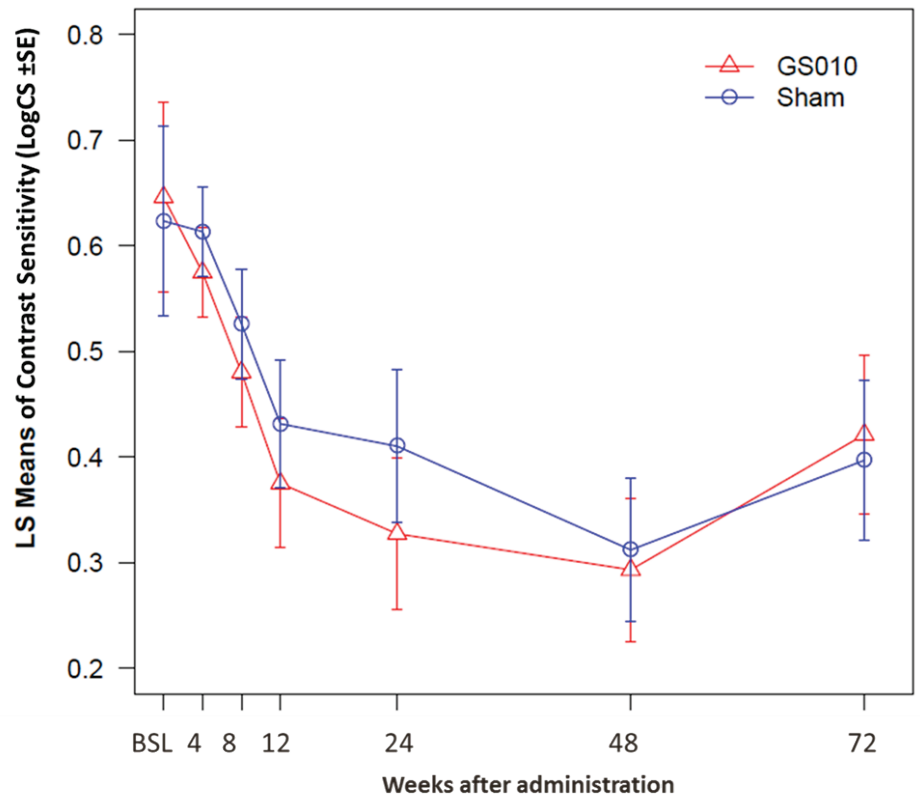
Visual Acuity bilaterally improved by +21 and +22 ETDRS letters from nadir to week 72 in GS010- and sham-treated eyes, respectively, although VA was still below baseline for both groups of eyes at week 72 (-10 and -11 ETDRS letters, respectively)



Mean visual acuity (BCVA) among GS010-treated eyes and sham-treated eyes evolved with similar trajectories, worsening to a lowest point, or nadir, before significantly improving to week 72 – coherent with REVERSE

Contrast Sensitivity: RESCUE 72-week

Bilateral contrast sensitivity evolved similarly to BCVA: while values for GS010-treated eyes and sham-treated eyes remained below baseline, CS also recovered so that the difference with baseline diminished at Week 72 compared to Week 48.



Responder Analysis: RESCUE 72-week

- **40% of eyes, both GS010-treated and sham-treated**, achieved a clinically meaningful BCVA improvement from nadir (-0.3 LogMAR or +15 ETDRS letters) at Week 72.

- **58% of GS010-treated and 50% of sham-treated eyes** achieved a clinically meaningful BCVA improvement from nadir (-0.2 LogMAR or +10 ETDRS letters) at Week 72.

"This improvement in visual function from Week 48 to Week 72, both in visual acuity and contrast sensitivity, strengthens our belief in the benefits of GS010, looking at the shift of the mean BCVA from off-chart to on-chart at Week 72. These results show a more favorable trend than the outcome we usually observe in clinical practice for LHON ND4 patients."

Dr. Catherine Vignal

Head of the department of Neuro-Ophthalmology at the Rothschild Foundation, Principal Investigator at the Department of Ophthalmology at *Centre Hospitalier National d'Ophtalmologie des XV-XX*, Paris

Bilateral improvements in visual function corroborate previously observed parallel evolution of GS010- and sham-treated eyes in both RESCUE and REVERSE trials

Retinal Anatomy: RESCUE 72-week

Anatomic outcomes so far do not indicate differential protection for the anatomy of GS010-treated eyes

In both drug-treated and sham-treated eyes, the relevant anatomy, as shown by various OCT measurements (tRNFL thickness, PMB thickness, GCL volume), continued to thin at Week 72, although the rate of thinning decreased between Week 48 and Week 72

"By design, the population in Rescue is very heterogeneous, and the structure of their retina is also highly variable, from marked atrophy of nerve fibers to edema. At unmasking, which happens after week 96, we will separate our subjects by their baseline OCT findings. In the sub-group with edema, thinning over time will be a good finding. In those with baseline atrophy of nerve fibers, increases in thickness will be a good sign. This mix of OCT findings at entry masks the true OCT findings at week 72 in Rescue."

Dr. Robert C. Sergott

Director, Wills Eye Hospital, Neuro-Ophthalmology and Director, William H. Annesley, Jr, EyeBrain Center, Thomas Jefferson University, Philadelphia, PA

Anatomic measures showed similar trajectories for GS010-treated and sham-treated eyes – difference not statistically significant at Week 72

Visual Acuity: Improvement from Baseline

REVERSE: Continuous bilateral improvement of Visual Acuity up to Week 96
RESCUE: Worsening VA compared to baseline reflects brutal progression of LHON

REVERSE 6-12 MONTHS	Change from BASELINE					
	Week 72			Week 96		
LS Mean (SE) [a]	**n**	**LogMAR**	**ETDRS Letter Equivalent**	**n**	**LogMAR**	**ETDRS Letter Equivalent**
GS010 Eyes	37	-0.294 (0.063)	+15	37	-0.308 (0.068)	**+15**
Sham Eyes	37	-0.246 (0.063)	+12	37	-0.259 (0.068)	**+13**

RESCUE 0-6 MONTHS	Week 48			Week 72		
LS Mean (SE) [a]	**n**	**LogMAR**	**ETDRS Letter Equivalent**	**n**	**LogMAR**	**ETDRS Letter Equivalent**
GS010 Eyes	36	+0.380 (0.129)	-19	34	+0.192 (0.104)	**-10**
Sham Eyes	36	+0.392 (0.129)	-20	33	+0.216 (0.104)	**-11**

[a] Primary Endpoint was assessed using a mixed model of analysis of covariance (ANCOVA) was used with change from baseline at week 48 as the response, and subject, eyes of the subject as random factor, treatment and the baseline LogMAR value as covariates in the model.

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Visual Acuity: Recovery from Nadir

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

Mean (SD) [b]	Change from NADIR [a]					
	Week 72			Week 96		
	n	LogMAR	ETDRS Letter Equivalent	n	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	37	-0.548 (0.435)	+27	37	-0.561 (0.439)	**+28**
Sham Eyes	37	-0.451 (0.509)	+23	37	-0.463 (0.489)	**+23**

Mean (SD) [b]	Week 48			Week 72		
	n	LogMAR	ETDRS Letter Equivalent	n	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	36	-0.257 (0.358)	+13	34	-0.413 (0.527)	**+21**
Sham Eyes	36	-0.236 (0.319)	+12	33	-0.435 (0.501)	**+22**

[a] NADIR: Nadir was defined as the **lowest post-baseline Visual Acuity** value up to Week of interest. LP/NLP vision was not included in the analysis.

[b] Mean change from nadir was calculated using observed values (no data were imputed).

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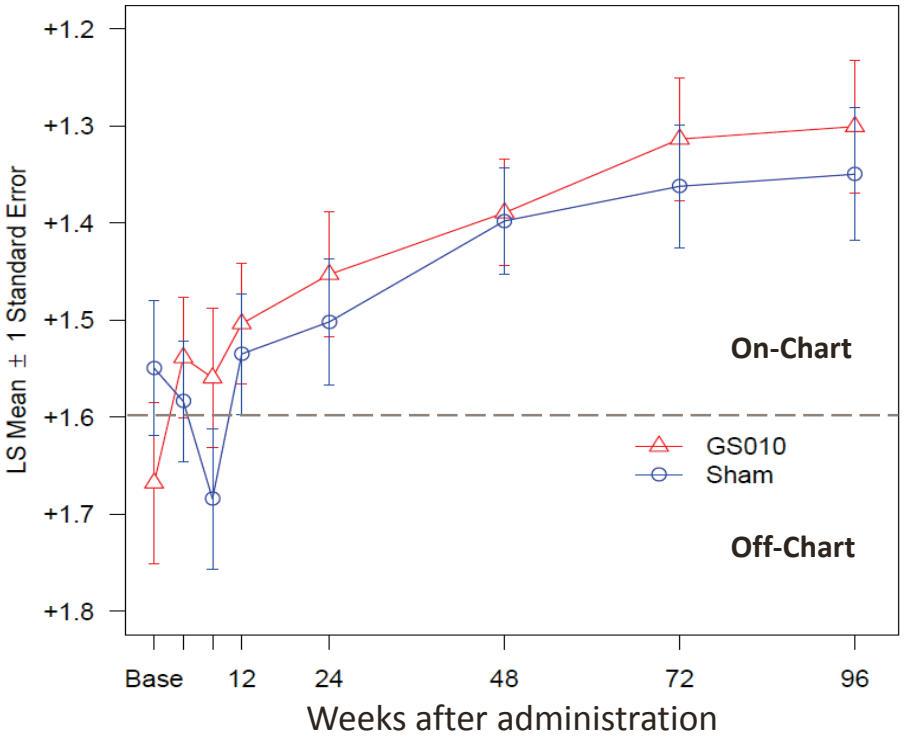
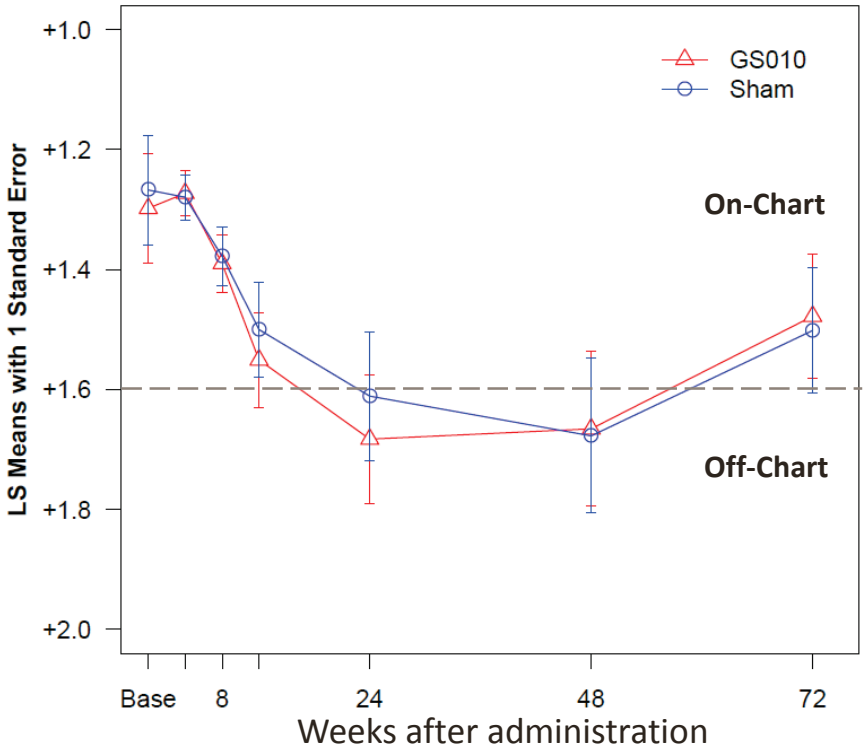
Visual Acuity: Time Course in LogMAR values

Bilateral improvement post Nadir





LogMAR All eyes Baseline	GS010 1.67 (0.50)	Sham 1.55 (0.42)	All 1.61 (0.46)

LogMAR All eyes Baseline	GS010 1.31 (0.52)	Sham 1.27 (0.62)	All 1.29 (0.57)

Safety: REVERSE & RESCUE

Favorable safety and tolerability profile

- No serious adverse events in GS010-treated eyes
- No discontinuation in the trial
- Most common ocular AEs were considered related to injection procedure, except for intraocular inflammation (accompanied by elevated intraocular pressure in some patients)
- Such episodes were without sequelae and responded to conventional treatment

GS010 was well-tolerated through 96 weeks after injection

Efficacy key findings: REVERSE & RESCUE

REVERSE: 96-Week

- **Sustained bilateral improvement in visual acuity (BCVA) at Week 96**
  - Versus baseline: **+15 ETDRS letters** equivalent in GS010 eyes and +13 ETDRS letters equivalent in sham eyes
  - Versus nadir: **+28 ETDRS letters** equivalent in GS010 eyes and +23 ETDRS letters equivalent in sham eyes
- **GS010-treated eyes achieved** favorable **treatment outcomes** at **higher rates** than sham eyes
  - Achieve BCVA gain of ≥ -0.2 LogMAR (+10 letters) versus baseline
  - GS010 eyes (65%) vs. sham-treated eyes (46%) - statistically significant difference
- 68% of REVERSE subjects attained **Clinically Relevant Recovery (CRR)** in at least one eye, **compared to 15% in a natural history study**
- Patients' **quality of life** scores continue to increase, especially in **ability to carry out vision-related activities**

RESCUE: 72-Week

- GS010 and Sham eye groups **track together at Week 72**
- **Bilateral improvement from nadir** of LogMAR VA by **+21 ETDRS letters** in GS010 eyes and **+22 ETDRS letters** in SHAM eyes, at Week 72
- **Bilateral improvement** of LogMAR VA from Week 48 to Week 72:
  - Mean VA went from off-chart at Week 48 to on-chart at Week 72
  - Mean change from baseline: both groups gained 2 lines from week 48 to week 72
- **Bilateral improvement** of contrast sensitivity from Week 48 to Week 72

REFLECT Phase III trial: assess efficacy and safety of bilateral injection

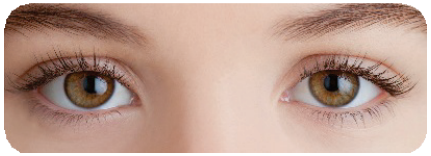
Double-masked, confirmatory study under Special Protocol Assessment from FDA

Patient inclusion criteria

- **90 patients** planned (45 in placebo group) with vision loss ≤ 1 year
- **Initiation:** 4Q 2017 (1st patient treated in March 2018)
- Recruitment expected to be completed in Q2 2019

Design

Group 1



GS010 in first affected eye

GS010 in second affected eye

First affected eye always treated with GS010

Second affected eye randomized between GS010 and placebo

GS010 in first affected eye

Placebo in second affected eye

Group 2

Endpoints at Week 48

Primary

- Difference in change of vision compared to baseline between GS010 Treatment vs. Placebo in second affected/not yet affected eyes
  (LogMAR visual acuity used for statistical analysis)

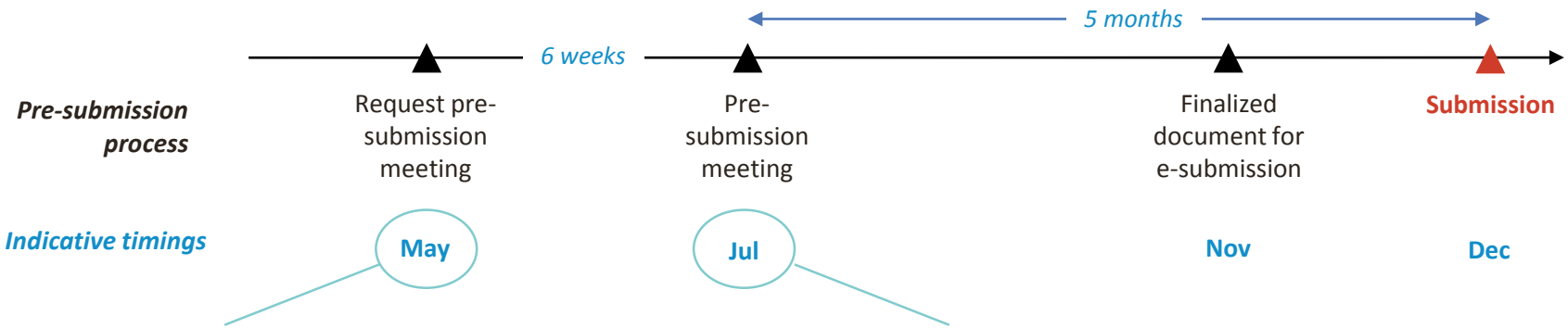
Secondary

- Best Corrected Visual Acuity at 2 years
- Spectral domain OCT biomarkers
- Humphrey visual field analysis
- Pelli Robson Low Vision Contrast Sensitivity
- Quality of life assessments

Source: Company

Engagement with EMA

Preparing for submission



Topics to be prepared

- Draft overviews for clinical, non-clinical and CMC data
- Draft SmPC, patient information leaflet, packaging
- Pediatric updates
- Information related to Conditional Marketing Authorisation and orphan market exclusivity
- Pharmacovigilance and other risk management aspects

Outcomes

- Assigned rapporteur
- Administrative guidance for dossier

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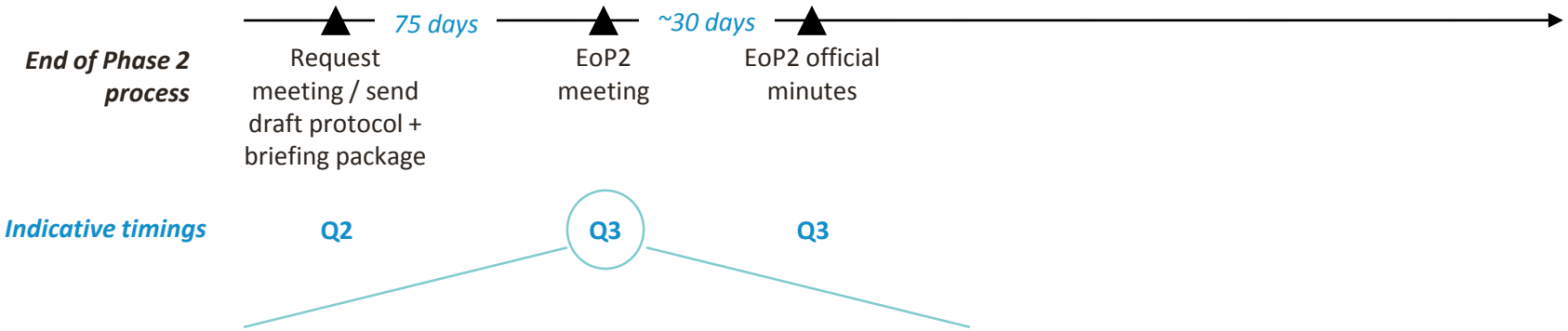
Engagement with FDA

Type B meeting to provide updates



Clinical updates

- **Objective**: provide updates relevant to clinical strategy
- **Topics**
  - REVERSE and RESCUE results to date
  - Implications for REFLECT
  - Investigations into contralateral effect
  - Potential new study with a more robust control arm

CMC updates

- **Objective**: provide updates on CMC
- **Topics**
  - Comparability protocol
  - Update on potency assay
  - Align on data to be available at time of submission
  - Discuss further data needs

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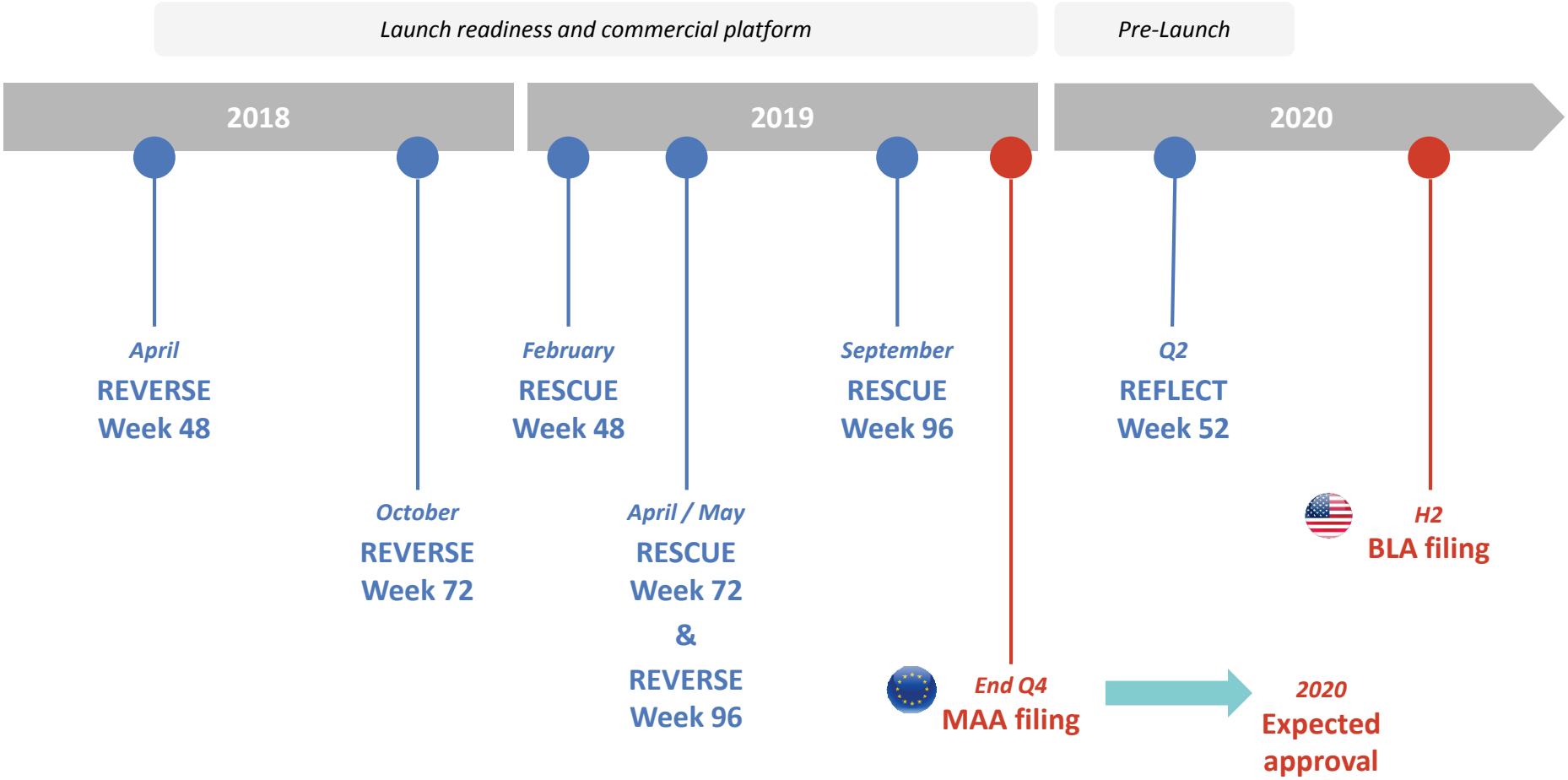
GS010 Path to Market



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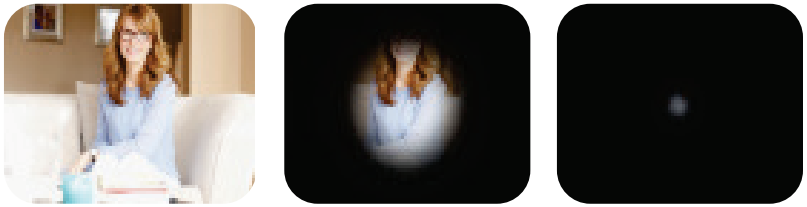
GS030

Second lead product candidate targeting photoreceptor degenerative diseases (RP/AMD)

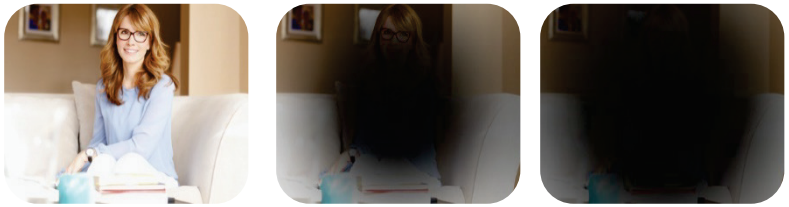
GS030 aim: treat degenerative diseases of photoreceptors that lead to blindness

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
- AMD strikes 350-400,000 new patients a year, most of them at 55-60 years of age
- 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

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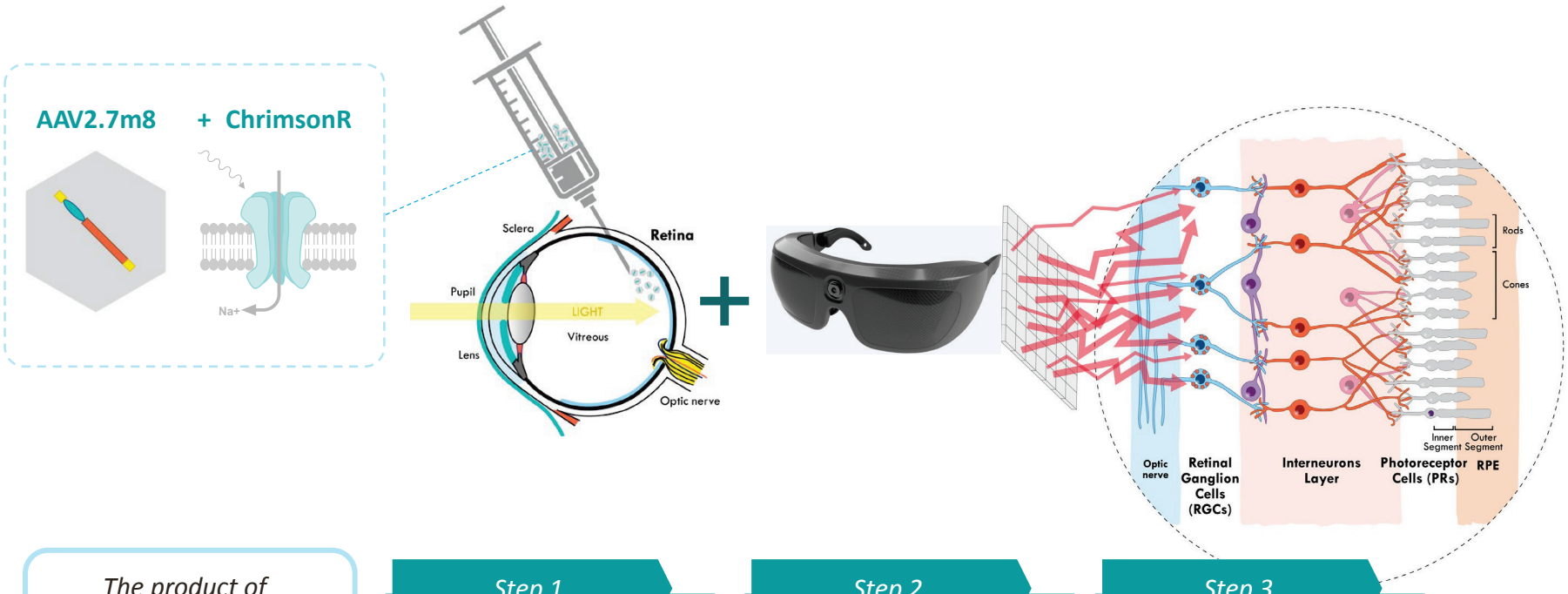
Optogenetics using GS030: gene therapy-based approach to restore light sensitivity



The product of research collaboration with

Massachusetts Institute of Technology

ADVERUM BIOTECHNOLOGIES

UPMC

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

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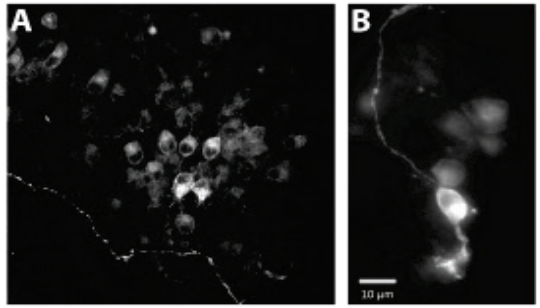
GS030: activated RGCs provide visual information to the higher visual centers

Localization of light-sensitive protein in NHP retina

Expression of ChrR-tdT in midget cells of monkey perifovea

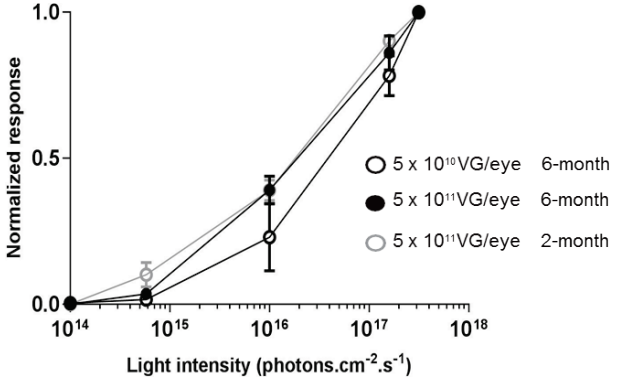
In vivo in NHP assessment 6 months after IVT injection



Dose-ranging response to firing relationship in NHP

Active dose range : 5x10^{10} and 5x10^{11} VG/eye

MEA assessment 6 months after IVT injection in NHP

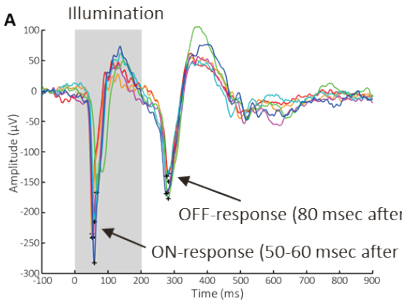


Restoration of a functional vision in P23H rats

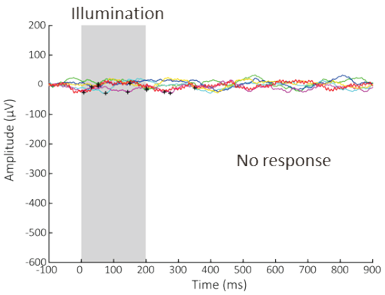
Light-induced visual evoked cortical responses

Full field 590 nm light from ~ 4.7x10^{15} to 1.1x10^{17} photons/cm^2/sec

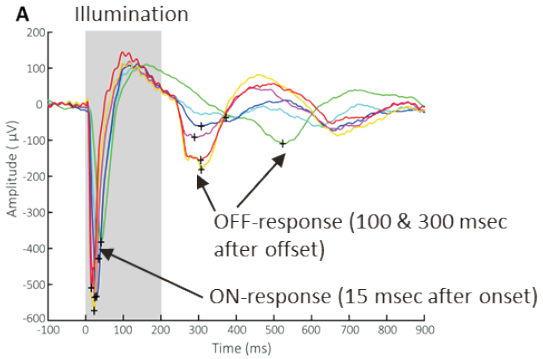
Normal Long-Evans rat



Untreated P23H rat



GS030-treated P23H rat



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GS030: well-tolerated and safe in pre-clinical studies

Toxicity study of GS030 product in non-human primates *(n=32)*

Bilateral IVT administration with vehicle vs $7.21x10^{10}$ VG/eye (low dose) vs $7.84x10^{11}$ VG/eye (high dose) in 100 µL

Ophthalmology

- **Dose-dependent ocular inflammation** in the anterior segment and vitreous, improving/resolving from Month 2 up to Month 6
- **Not associated with any retinal tissue destruction** or functional changes
- **No or very slight residual inflammation** in all animals at 6 months (**self-resolution**, no treatment before or after injection)

Histology

- **Dose-dependent minimal mononuclear cell infiltration** in eye tissues
- **No histological findings in other tissues**

Immunogenicity (anti-AAV2 NAb)

- **Expected humoral immune response** in serum starting at Day 15; tended to decrease at Week 13 then sustained up to Month 6
- **Dose-dependent local immune response** in aqueous humor and vitreous

Local tolerance of GS030 product with light exposure in rd1 blind mice *(n=36)*

Bilateral IVT administration with vehicle vs $7.84x10^{9}$ VG/eye in 1 µL; 590 nm LED light at $1.4×10^{16}$ vs $1.7×10^{17}$ photons/cm^2/s vs ambient room light

Local tolerance

- **No ophthalmic findings** related to gene therapy (GS030-DP) or to LED light
- **No microscopic findings** in the retina related to GS030-DP or to LED light
- **Transient corneal edema & lens opacity** linked to anesthesia procedure

ChrimsonR-tdTomato expression

- **Good expression** of ChrimsonR-tdTomato in retinas and optic nerves

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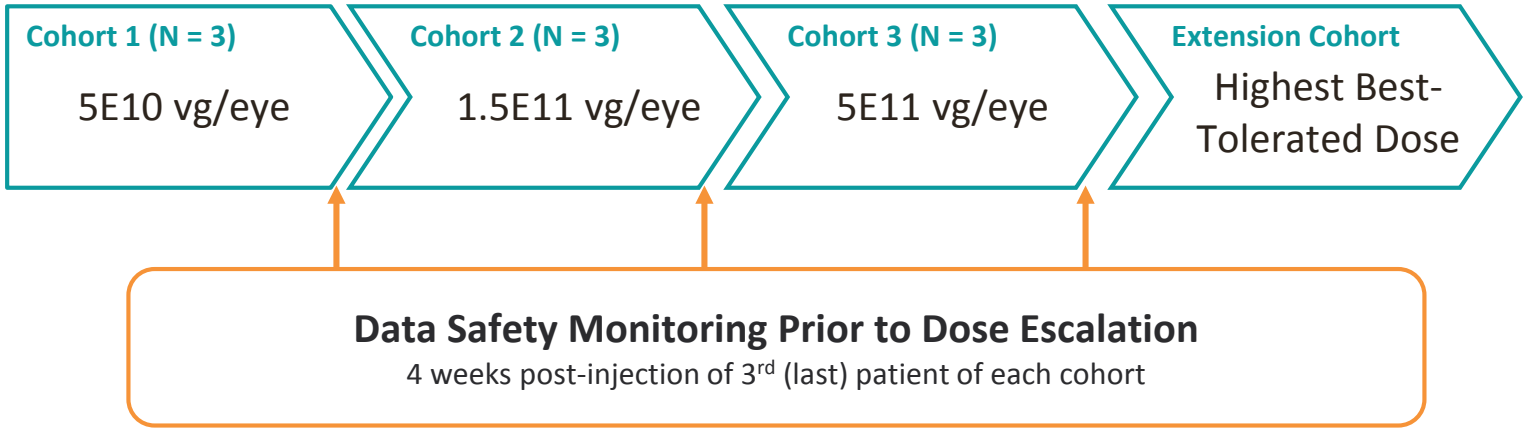
PIONEER Phase I/II clinical trial: A First-in-Man study

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

1st DSMB recommended to continue with cohort 2 without modification on April 30, 2019

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GS030: CMC progress & Regulatory interactions

CMC

- **Manufacturing process developed up to 25L**
  - Toxicology batch produced at 25L scale
  - Drug Substance titers (> 2E13 vg/ml) and characteristics in line with expectations
  - Scale up to 100L batch successful
- **Manufacturing process successfully transfered to GMP**
  - GMP clinical supply ready
  - 100L GMP batches manufactured
- **Potency assay**
  - Development completed
  - Transfer in progress

Regulatory

- **Orphan Drug Designation** granted in the US and in Europe
- **Active strategy & interactions with US and EU Agencies** to obtain advice on preclinical package to support FIM and exploit the existing process of expedited programs
- **CTA approved in the UK and in France**
- **IND released by FDA in the US**

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GS030 Key Milestones

Pivotal trial expected to be initiated in 2020

2016-2017

CTA

Orphan Drug Designation in US and EU

2018

CTA IND

October

PIONEER FIM

2019

PIONEER GS030 STUDY

Early findings from first patients in PIONEER

2020

Completion of patient enrollment

PIONEER Preliminary Results

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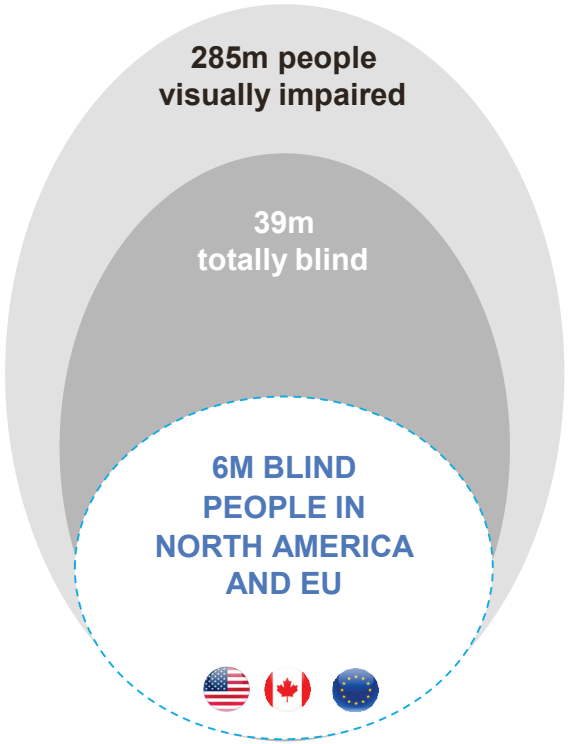
Building high strategic value

Curing blindness represents major market opportunity

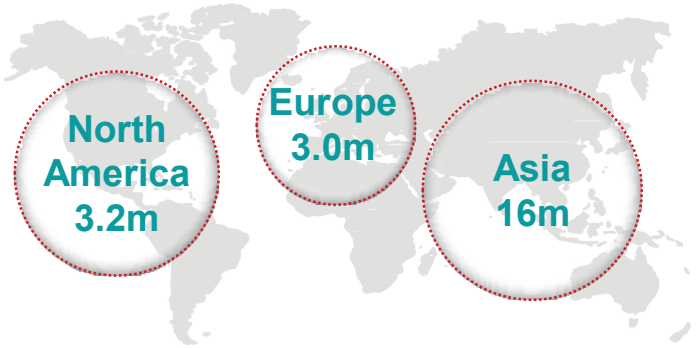


Source: WHO, IAPB-VISION2020, NORC-Univ. of Chicago / The Economic Burden of Vision Loss and Eye Disorders in the United States, 2014.

Favorable reimbursement conditions:

- Gene therapy in ophthalmology for rare diseases could be considered **similar to organ transplants for payers**
- Blindness imposes a **high burden** on health systems
  - Total blindness costs exceed tens of billions USD per annum
- **Absence of curative treatments**
  - Increasing pressure from patients and patients associations

Geographical Split – Blind people in major markets



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Pricing and reimbursement environments are evolving to accommodate curative potential of innovative cell and gene therapies

Early entrants are setting pricing and contracting benchmarks, and authorities signal flexibility to new thinking

LUXTURNA™ voretigene neparvovec-rzyl for subretinal injection

- Approved December 2017 for treatment of biallelic RPE65 mutation-associated retinal dystrophy
- List price: $425,000 *per eye*
- Early commercial agreements with select health plans
  - Pay-for-performance
  - Staggered payments
  - Special procurement process using specialty pharmacies
  - CMS policy (Medicare coverage) to be published in 2019

Strimvelis

- Approved May 2016 for treatment of ADA-SCID
- List price: 594,000€ *per patient*
- Positive HTA assessments in UK and IT; covered by ***EU Directive 2011/24****
  - Treatment administered only at the designated treatment center in Milan

Note: Luxturna received marketing authorization for Europe in November 2018 but a list price has not yet been published.

+ Openness to alternative pay-for-performance / risk-sharing options among individual plans
+ Industry consultation into legislative initiatives covering new payment models for regenerative therapies

+ Ongoing cross-border initiatives in the EU, e.g., European reference networks (ERN EYE for ophthalmology)
+ HTA-industry consultations on refining cost effectiveness models for curative treatments

*The directive sets out the conditions under which a patient may travel to another EU country to receive medical care and reimbursement. It covers healthcare costs, as well as the prescription and delivery of medications and medical devices.

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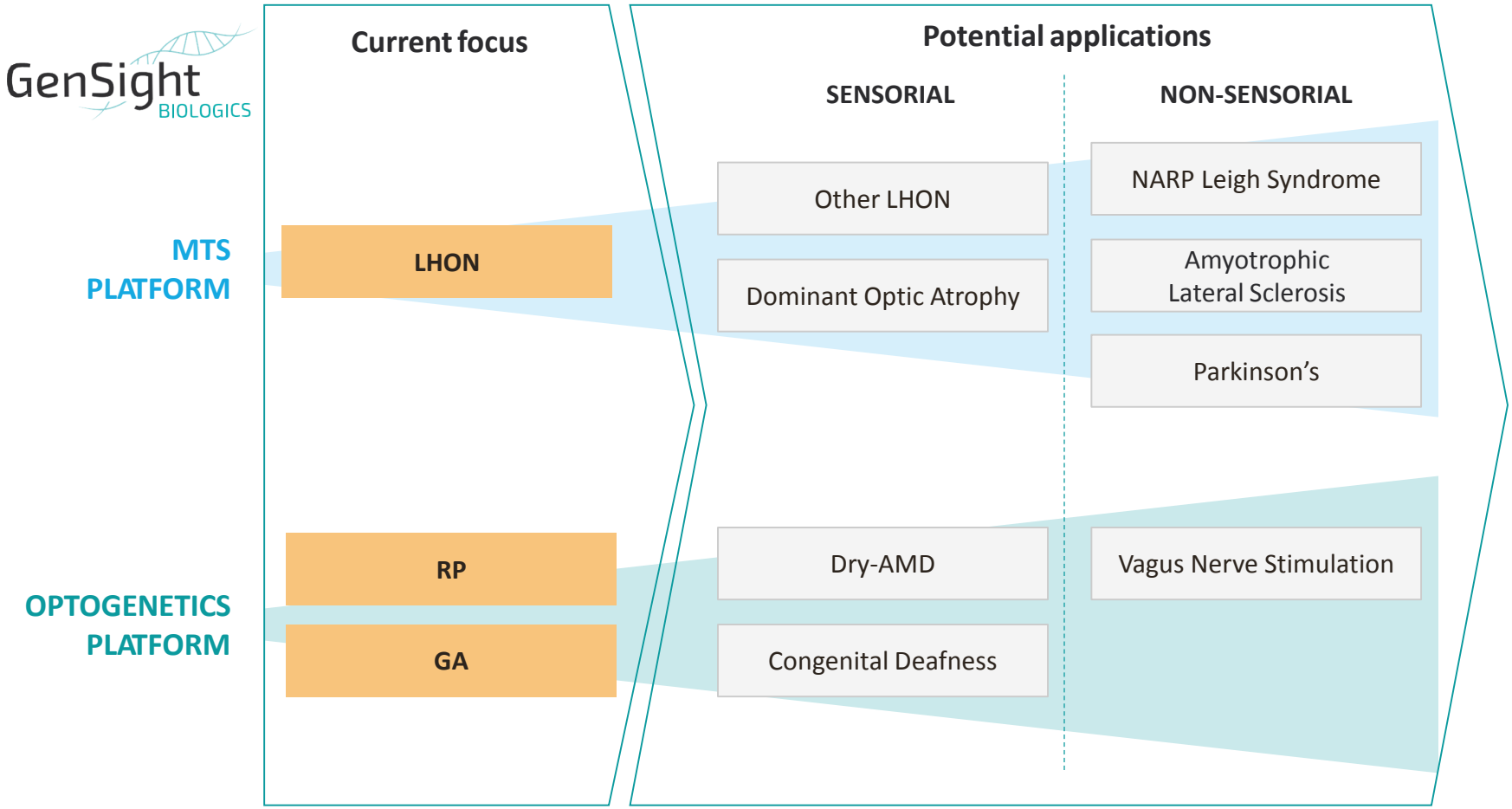
Potential applications of GenSight technology platforms



Ability to leverage technology platforms and significant expertise to expand the pipeline in ophthalmology and other neurodegenerative disorders

GenSight Biologics

Key financial information

Financing history

- March 2013 – Series A round – €20m
- June 2015 – Series B round – €32m
- July 2016 – Euronext IPO – €45m
- June 2017 – PIPE – €22m
- February 2019 – PIPE – €8m

Listed on Euronext Paris (SIGHT)

- Established in 2012, IPO in July 2016

Recognition from Blue-Chip specialist investors

- Perceptive, Fidelity, Abingworth, Versant, Sofinnova, JP Morgan AM and others

Analyst coverage

- Oddo & Cie – Martial Descoutures (FR)
- Gilbert Dupont – Jamila El Bougrini (FR)
- Chardan – Gbola Amusa (US)
- NIBC – Dylan van Haaften (NL)

Cash position
(as of Mar 31, 2019)

€24.0m

Number of outstanding shares

28.7m

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Appendix

RESCUE 72-week Follow-up Data

Key Findings

✓GS010 and Sham eye groups **track together at Week 72**

✓**Bilateral improvement from nadir** of LogMAR VA by **+21 ETDRS letters** in GS010 eyes and +**22 ETDRS letters** in SHAM eyes, at Week 72

✓**Bilateral improvement** of LogMAR VA from Week 48 to Week 96:

- Mean VA went from off-chart at Week 48 to on-chart at Week 72
- Mean change from baseline: both groups gained 2 lines from week 48 to week 72

✓**Bilateral improvement** of contrast sensitivity from Week 48 to Week 96:

- Mean change from baseline in GS010 eyes went from -0.34 to -0.25 LogCS
- Mean change from baseline in SHAM eyes went from -0.32 to -0.28 LogCS

REVERSE 96-week Follow-up Data

Key Findings

- ✓**Sustained bilateral improvement** in **visual acuity (BCVA)** at **Week 96**
  - **Versus baseline: +15 ETDRS letters equivalent** in GS010 eyes and **+13 ETDRS letters equivalent** in sham eyes
  - **Versus nadir: +28 ETDRS letters equivalent** in GS010 eyes and **+23 ETDRS letters equivalent** in sham eyes
- ✓**GS010-treated eyes achieved** favorable **treatment outcomes** at **higher rates** than sham eyes
  - **Achieve BCVA gain of ≥ -0.2 LogMAR (+10 letters) versus baseline**

    GS010 eyes (65%) vs. sham-treated eyes (46%) – statistically significant difference
  - **Achieve BCVA gain of -0.3 LogMAR (+15 letters) from on-chart visual acuity or avoid legal blindness (20/200)**

    GS010 eyes (32%) vs. sham-treated eyes (16%) – statistically significant difference
  - **Avoid legal blindness**

    GS010 eyes nearly four times more likely to avoid legal blindness – statistically significant difference
- ✓68% of REVERSE subjects attained **Clinically Relevant Recovery (CRR)** in at least one eye**, compared to 15%** in a **natural history** study
- ✓Patients' **quality of life** scores continue to increase in their **ability to carry out vision-related activities**
- ✓GS010 **well-tolerated and safe through 96 weeks** of follow-up after injection

Commercialization strategy

Three pillars for securing the launch and growth trajectory of GS010

Reimbursement at premium price

- Develop and communicate **compelling value proposition** to payers, physicians and patients
- Develop **coherent pricing strategy** supported by locally relevant **contracting approach and service offerings**
- Maintain **up-to-date insights** on European shifting reimbursement landscape

Efficient pathways to centers of excellence

- Drive **early, accurate diagnosis** of LHON patients
- Develop initiatives to **minimize friction in originations and referrals**
- Sustain **relevance** with neuro-ophthalmologist and patient communities

Lean and effective commercial organization

- Focus resources on the most critical **touchpoints with key customers**:
  - Select centers of excellence
  - Select medical conferences
  - Key patient advocacy groups
- Define **marketing mix** to amplify messages to broader ophthalmologist and neurologist audience
- Optimize **division of responsibilities** between internal team and external partners

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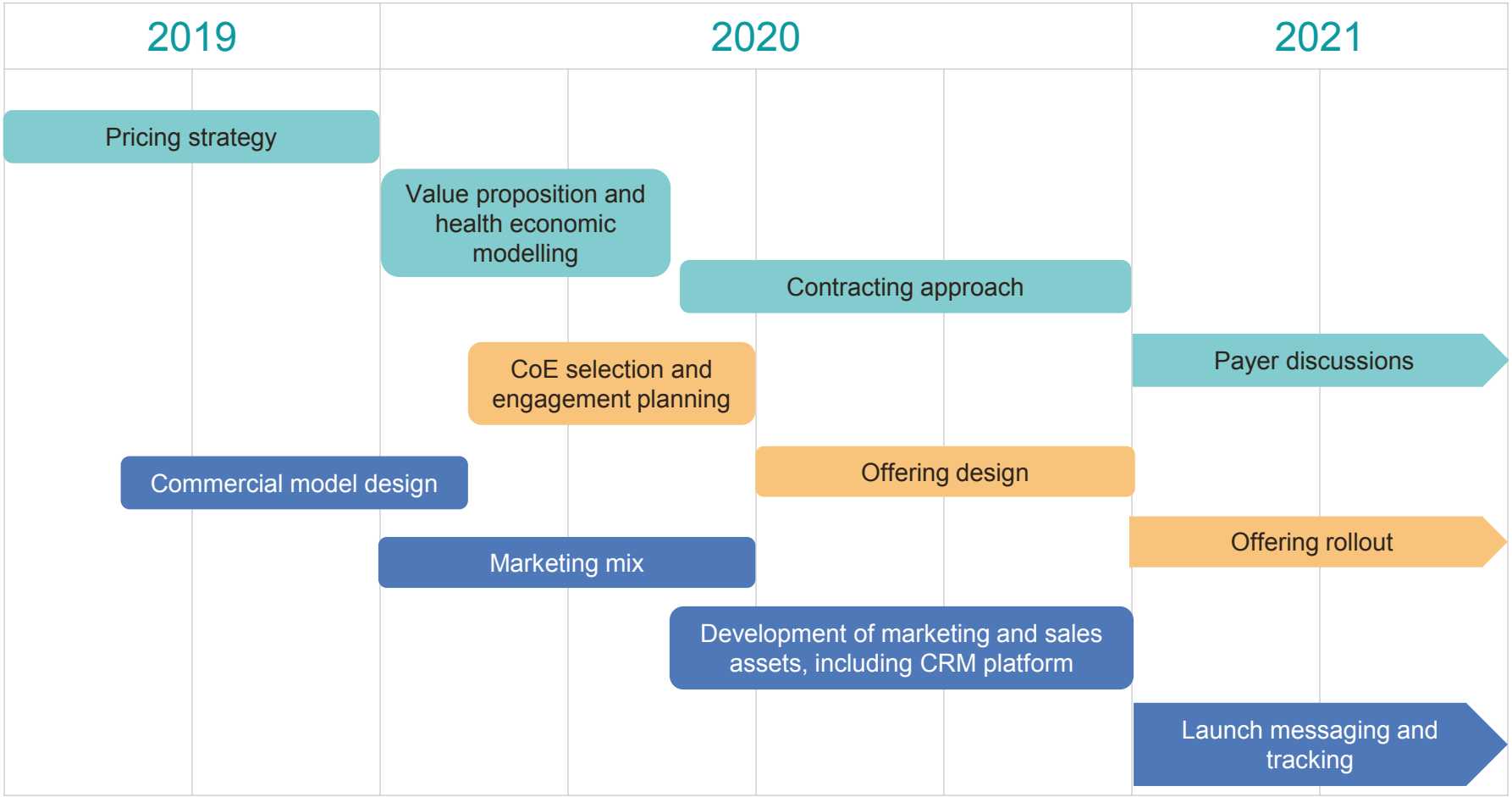
Overview of key initiatives to support commercialization strategy

Overview of commercialization preparations



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