



Corporate Presentation

February 2019

A LEADING GENE THERAPY BIOTECHNOLOGY COMPANY

GENSIGHT-BIOLOGICS.COM

Disclaimer

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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



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 Gidoïn
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

Our target: degenerative retinal diseases with underlying genetic causes

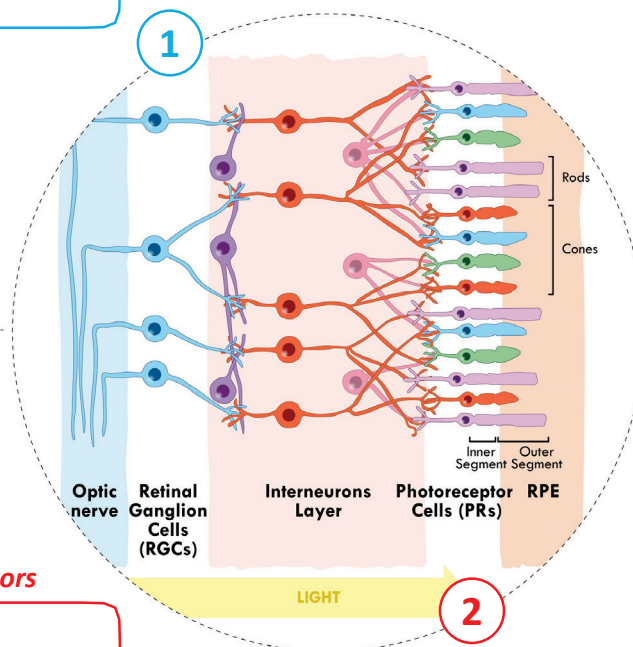
LEBER HEREDITARY OPTIC NEUROPATHY (LHON)

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

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) and Oct (72w) 2018. 96w expected in May 2019. RESCUE : Phase III top-line data reported in Feb 2019 (48w). 72w expected in Apr 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 enrolled 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 12 months away from MAA submission in Europe

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

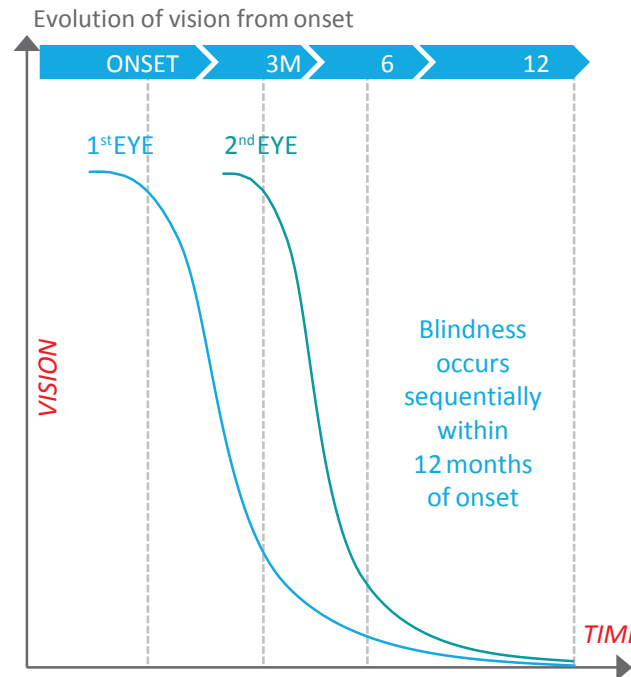
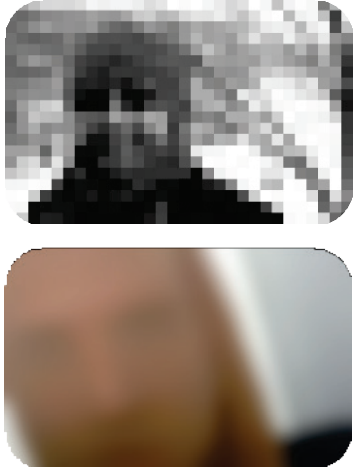


Image source: illustrated from Newam NJ et al., Am J Ophthalmom. 141(6), 1061-1067, 2006

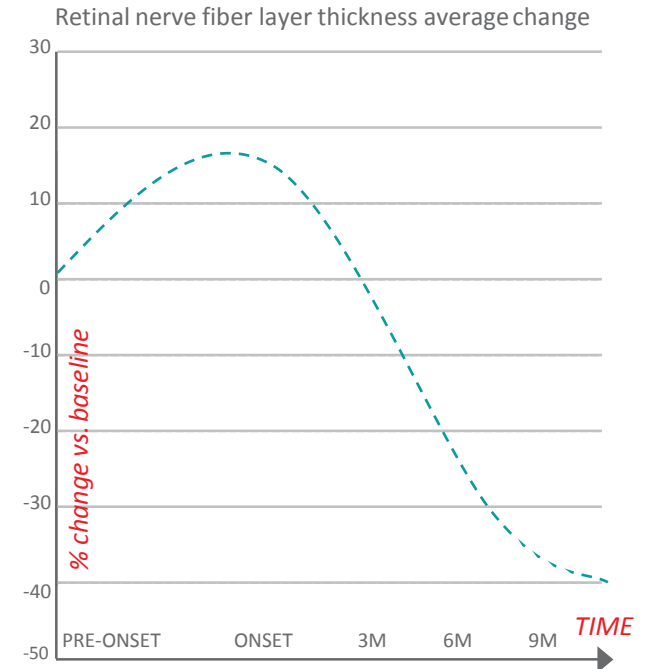


Image source: illustrated from Barboni et al Natural History of Leber's Hereditary Optic Neuropathy: An OCT Study

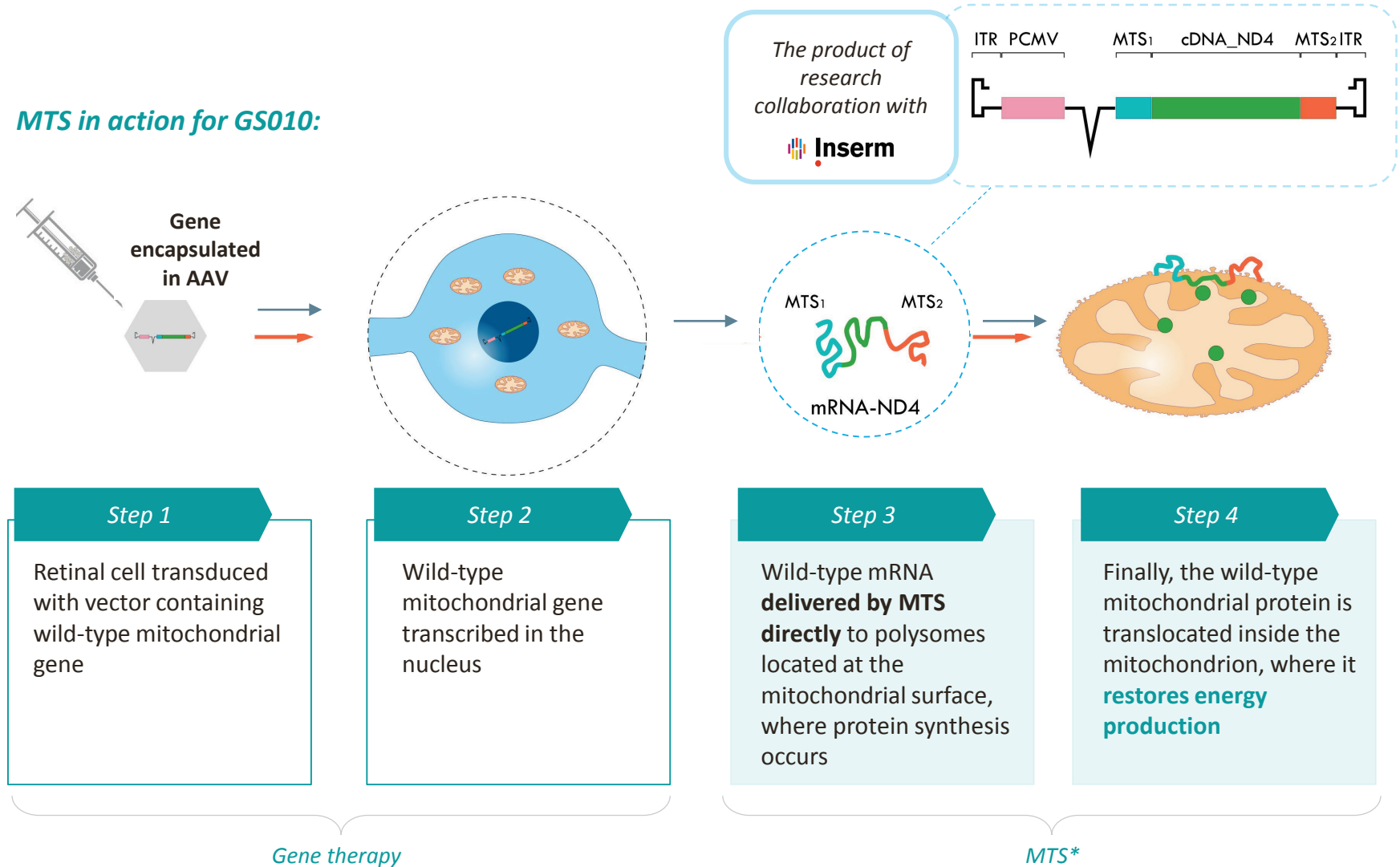


Incidence	0.15/100,000
Prevalence	1/31k-40k
Blindness	15-35y

- **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

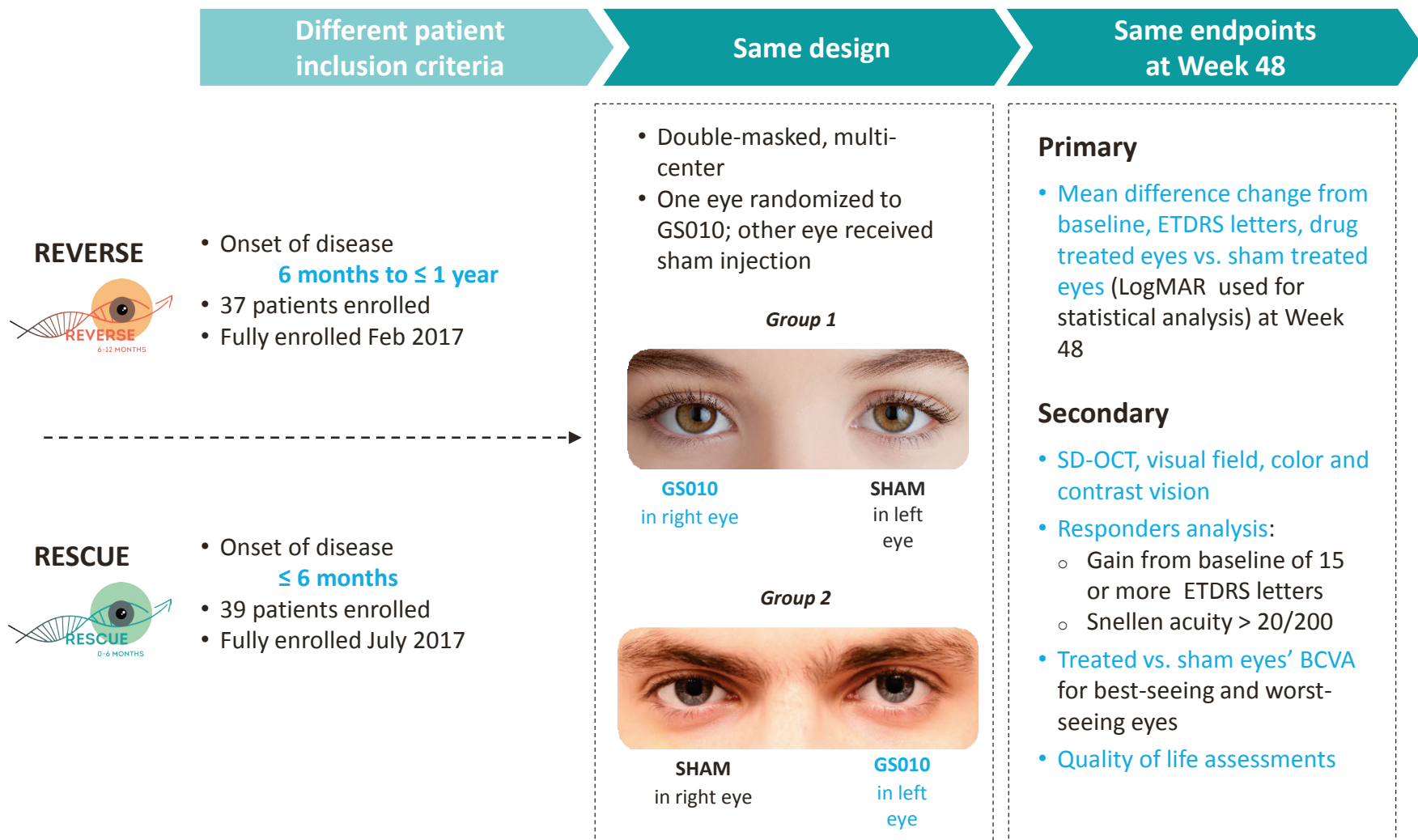
Solution: Gene therapy to produce working mRNA, with **MTS* technology** to shuttle mRNA directly to affected mitochondria

MTS in action for GS010:



RESCUE & REVERSE Phase III trials

Time-based strategy to assess GS010 efficacy

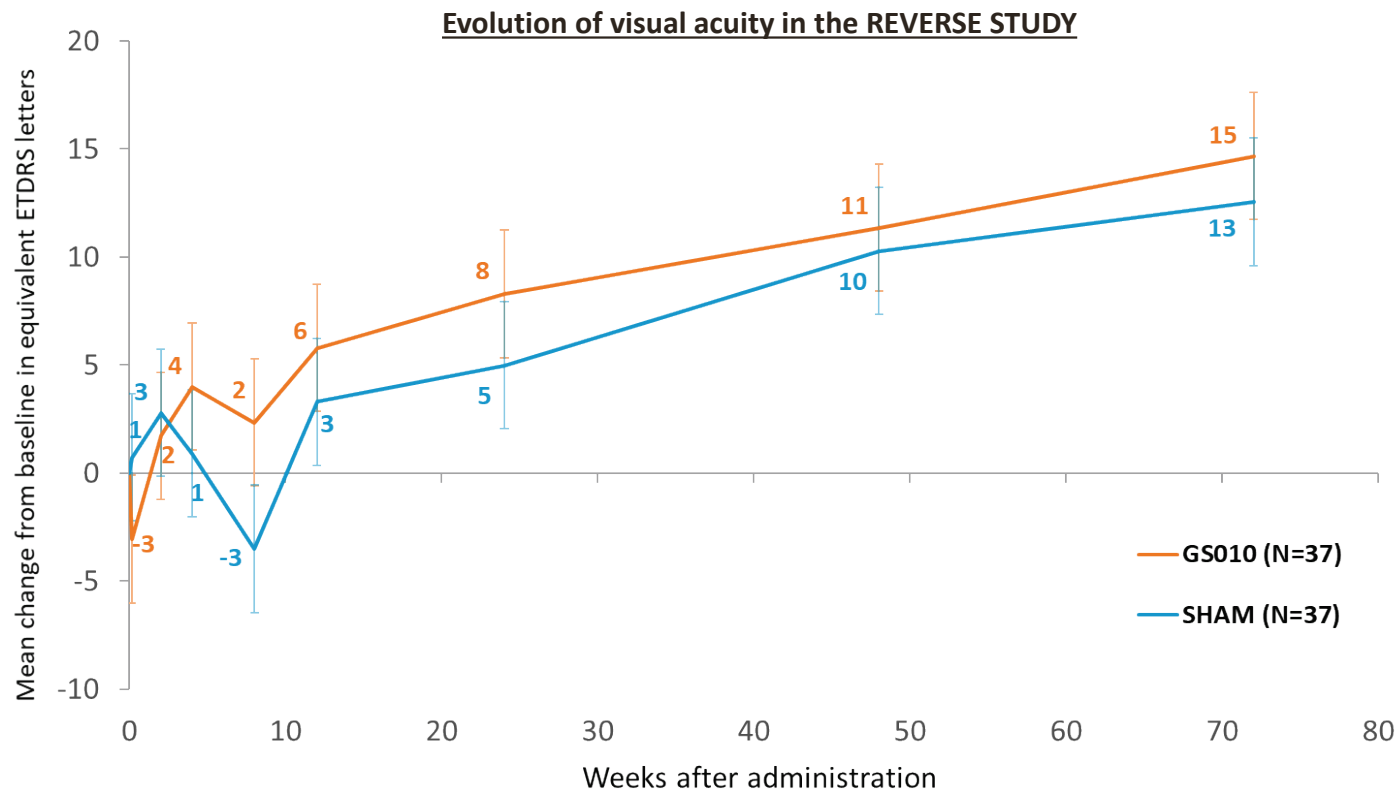


Source: Company

REVERSE Data at 72 Weeks: Improvement of central Visual Acuity

Sustained improvement of best-corrected visual acuity (BCVA), to clinically meaningful levels at Week 72

- A clinically meaningful improvement of +15 ETDRS letters reported in treated eyes
- A continuous bilateral improvement from Baseline to Week 72



REVERSE Data at 72 Weeks: Additional visual function outcomes

Improvement of Contrast Sensitivity

- **Contrast sensitivity** as determined by Pelli-Robson low contrast testing increased in both eyes from baseline to week 72:

Treated eyes: +0.21 LogCS

Untreated eyes: +0.15 LogCS

- Proportion of treated eyes that achieved a **clinically meaningful improvement of at least 0.3 LogCS** was statistically significantly higher than that of sham-treated eyes:

Treated eyes: 45.9%

Untreated eyes: 24.3%

$p = 0.0047$

GEE model predicting BCVA $\geq 20/200$

In a generalized estimating equation (GEE) model used to assess treatment effect on VA of $\geq 20/200$ acuity, GS010-treated eyes were significantly more likely to achieve 20/200 threshold than sham-treated eye.

$p = 0.0012$; *odd ratio* = 4.07

REVERSE Data at 72 Weeks: **Anatomic targets successfully engaged**

- SD-OCT demonstrated **statistically significant preservation** of retinal ganglion cells and **preservation** of retinal fiber layer in treated eyes vs. untreated eyes

- **Change from baseline in retinal ganglion cell macular volume measured:**

Treated Eyes	no loss
Untreated Eyes	-0.044 mm ³

p = 0.0060

- **Change from baseline in thickness of the papillo-macular bundle:**

Treated Eyes	+1.6 µm
Untreated Eyes	-1.4 µm

p = 0.0362

- **Change from baseline in thickness of the temporal quadrant of the retinal nerve fiber layer:**

Treated Eyes	-1.6 µm
Untreated Eyes	-3.6 µm

p = 0.0521

Sustained preservation of retinal anatomy in drug-treated eyes demonstrates neuroprotective effect of GS010

REVERSE Results at W72 – NEI VFQ-25

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 at Week 48 and Week 72**
- **Magnitudes of 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%
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.

Improvement from baseline at Week 72 for other sub-scales: social functioning: +2.4 (23.3%); ocular pain: +1.4 (5.6%); color vision: +5.6 (20.8%); peripheral vision: +1.4 (15.5%). Missing values for general health subscale. Driving questions not pertinent to LHON patients.

RESCUE 48-week Topline Data: Similar trajectories with nadir for visual acuity

Visual Acuity deteriorates to a low point before beginning to improve: **mean improvement from nadir to Week 48 of +13 and +11 ETDRS letter equivalent** in GS010- and sham-treated eyes, respectively

LS Mean (SE) ^a	Change from BASELINE to Week 48	
	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	+0.380 (0.129)	-19
Sham Eyes	+0.392 (0.129)	-20

^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.

Mean (SD) ^b	Change from NADIR^a to Week 48	
	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	-0.257 (0.358)	+13
Sham Eyes	-0.236 (0.319)	+11

^a NADIR: lowest visual acuity measure post-treatment.

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

- Worsening VA compared to baseline reflects brutal progression of LHON
- Worsening down to a nadir (lowest point of VA), then bilateral improvement
- As in REVERSE, visual acuity in GS010- and sham-treated eyes track together

RESCUE 48-week Topline Data

Responder analyses show outcomes in favor of GS010-treated eyes in subset of patients

- **GS010-treated eyes were significantly more likely to have 20/200 or better vision, the threshold for legal blindness** (statistically significant with $p=0.0347$; odds ratio = 2.9), than sham-treated eyes.
- **In 24% of subjects, change from baseline of high-contrast visual acuity in GS010-treated eyes was at least 0.3 LogMAR (15 ETDRS letters) better** than their sham-treated eyes.
- **In 24% of subjects, change from baseline of low-contrast acuity (measured on the Pelli Robson scale) in GS010-treated eyes was at least 0.3 LogCS better** than their sham-treated eyes.

Even at an early readout at Week 48, some trends point toward GS010 efficacy

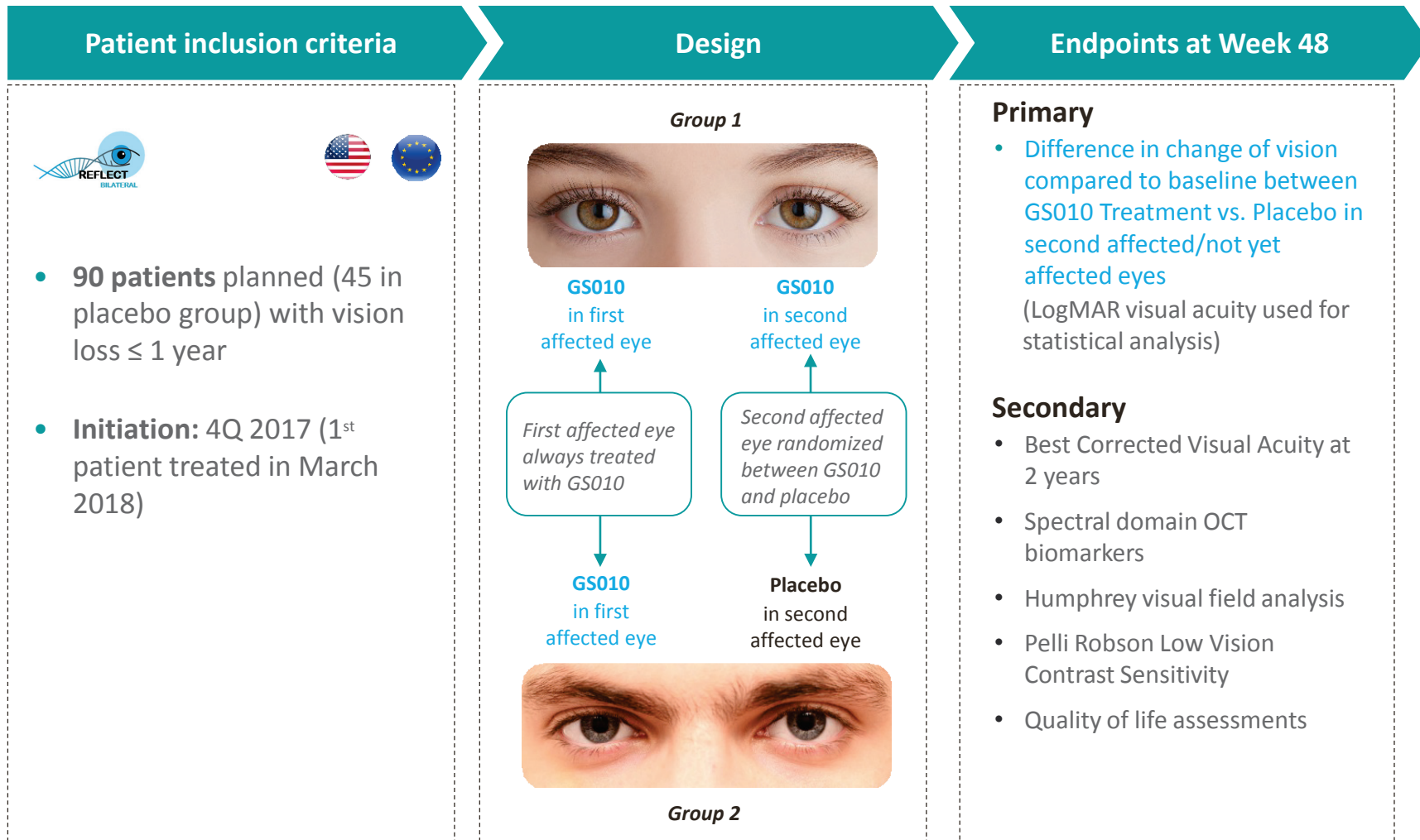
RESCUE & REVERSE safety data

Favorable safety and tolerability profile for GS010

- GS010 reported to be well-tolerated
- Ocular adverse events most frequently reported in the therapy group were mainly related to the injection procedure
- Occurrence of intraocular inflammation (accompanied by elevation of intraocular pressure in some patients) responsive to conventional treatment and without sequelae
- No withdrawals from the trial related to study drug or procedure

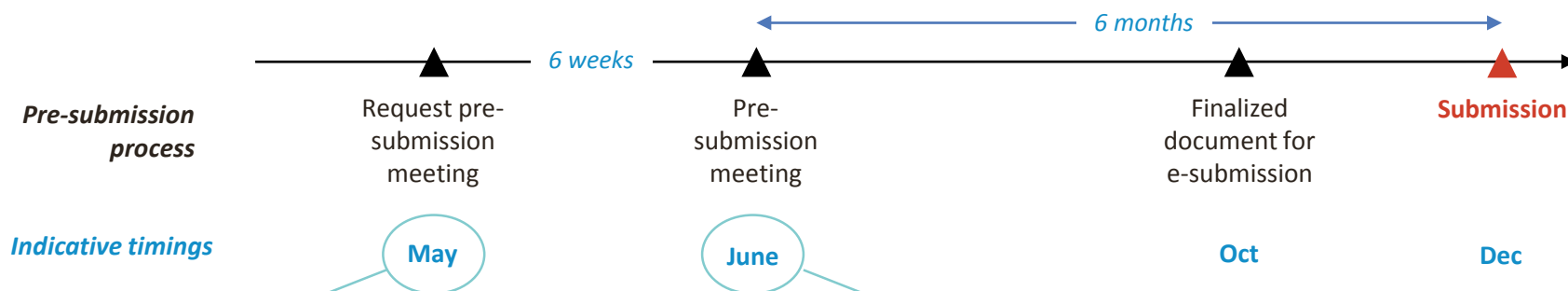
REFLECT Phase III trial: assess efficacy and safety of bilateral injection

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



Engagement with EMA

Preparing for submission



Topics to be prepared

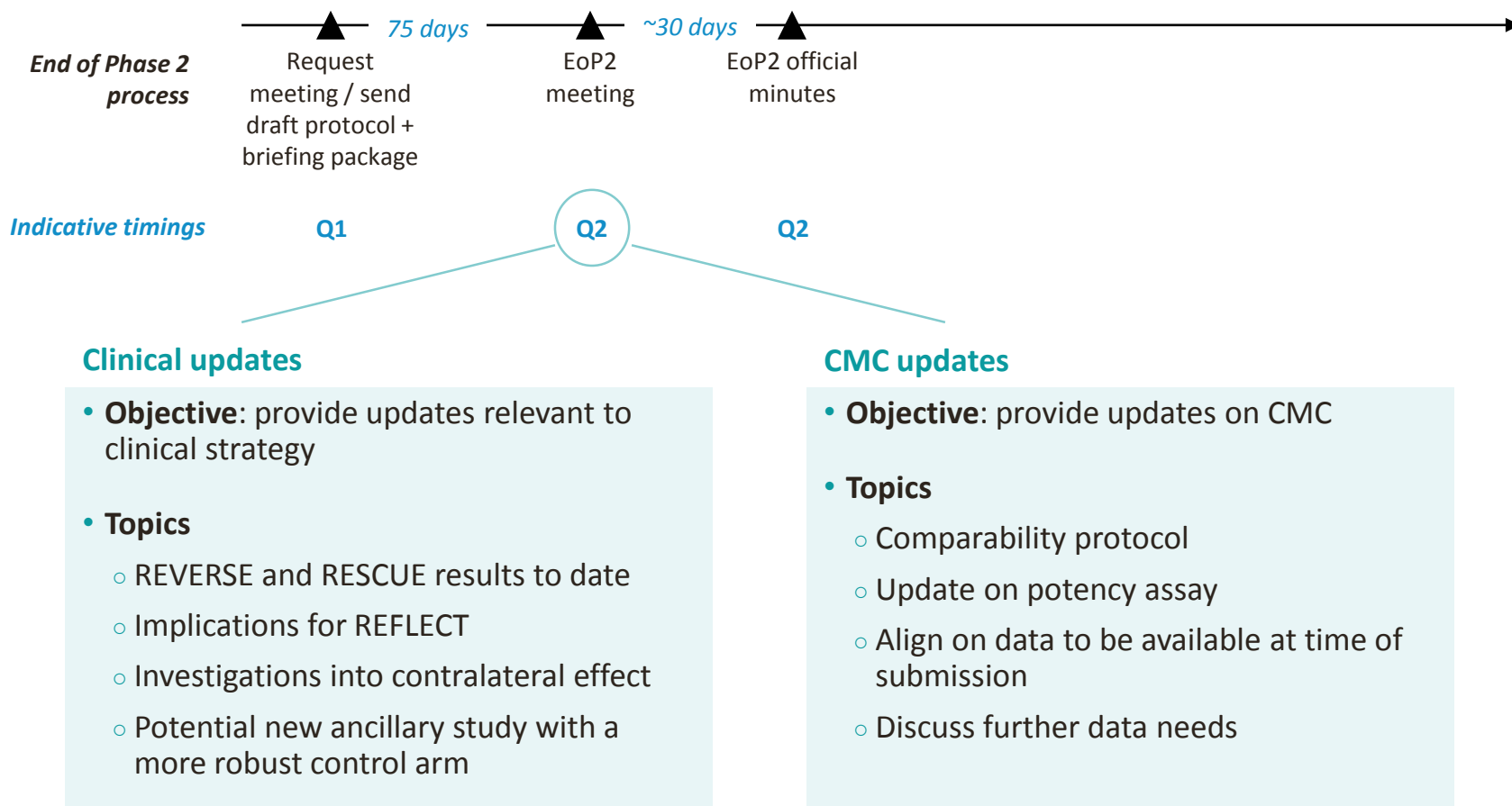
- Overviews for clinical, non-clinical and CMC data
- Draft SmPC, patient information leaflet, packaging
- Pediatric updates
- Information related to Conditional Marketing Authorisation and orphan market exclusivity
- Pharmacovigilance and other risk management aspects

Outcomes

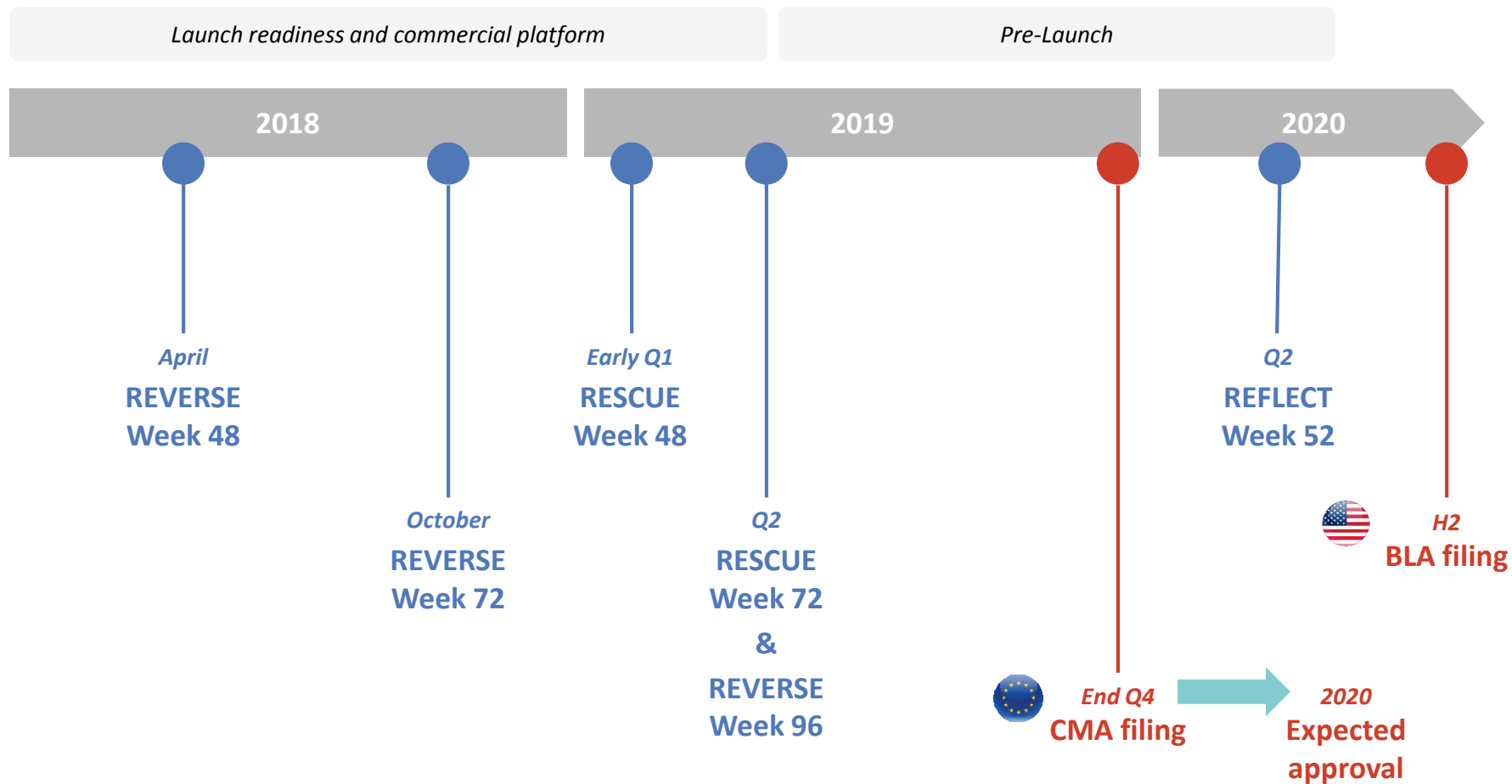
- Assigned rapporteur
- Administrative guidance for dossier

Engagement with FDA

End of Phase 2 (EoP2) meeting to provide updates



GS010 Path to Market



GS030

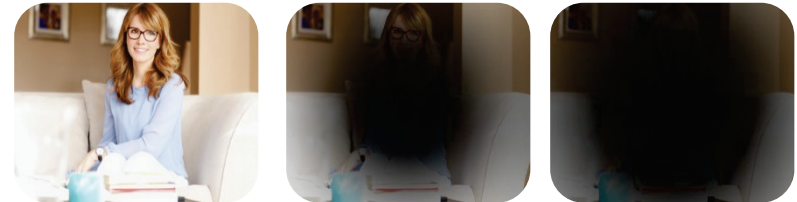
Second lead product
candidate targeting
photoreceptor degenerative
diseases (RP/AMD)

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

Retinitis Pigmentosa



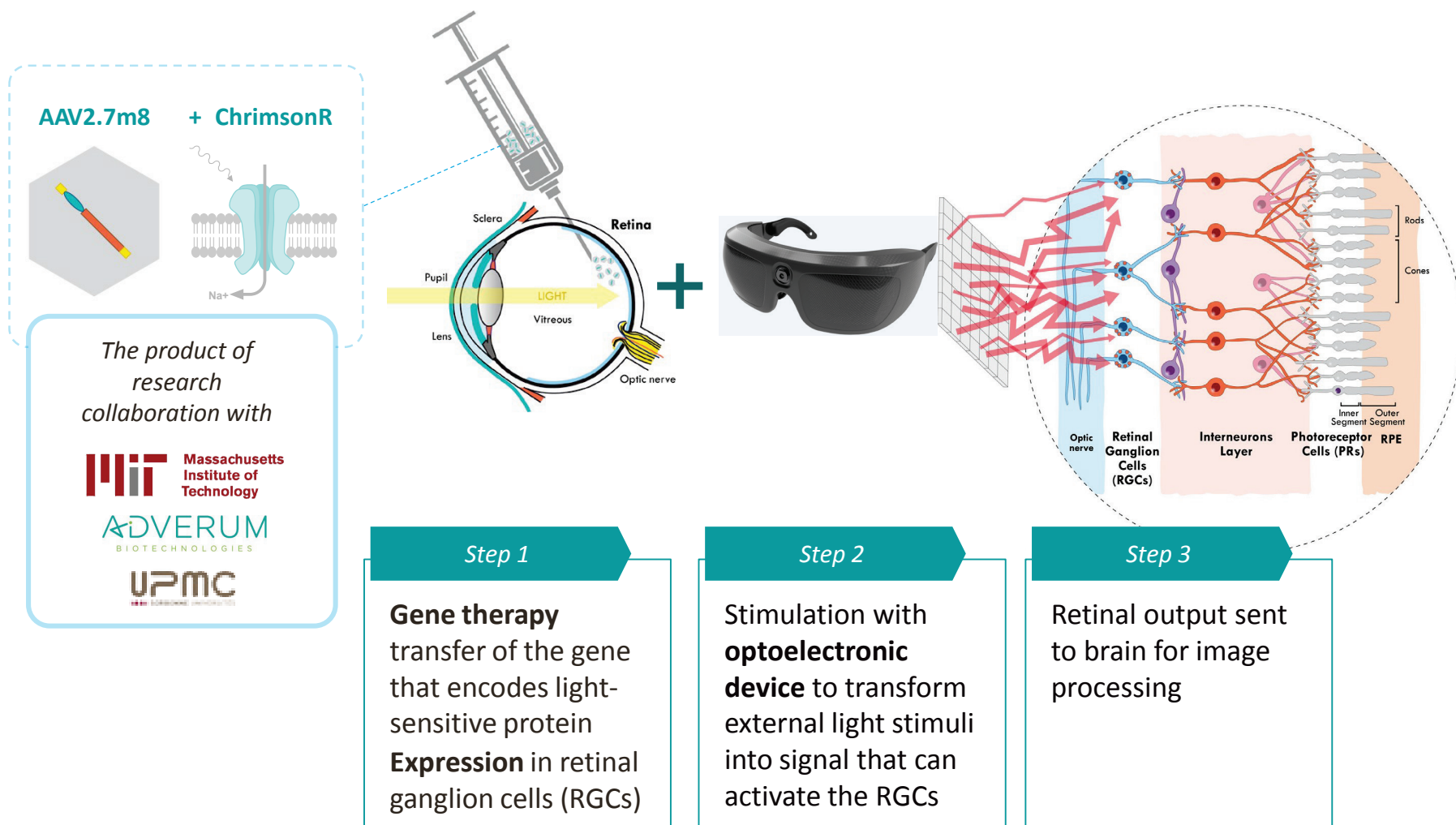
Geographic Atrophy (GA) in AMD (Age-Related Macular Degeneration)



- 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

- 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

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

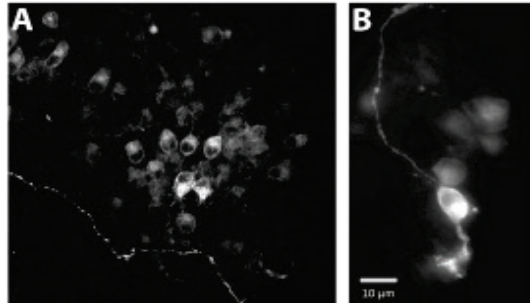


GS030: activated RGCs provide visual information to the higher visual centers

Localization of light-sensitive protein in NHP retina

Expression of ChrR-tdT in midget cells of monkey perfovea

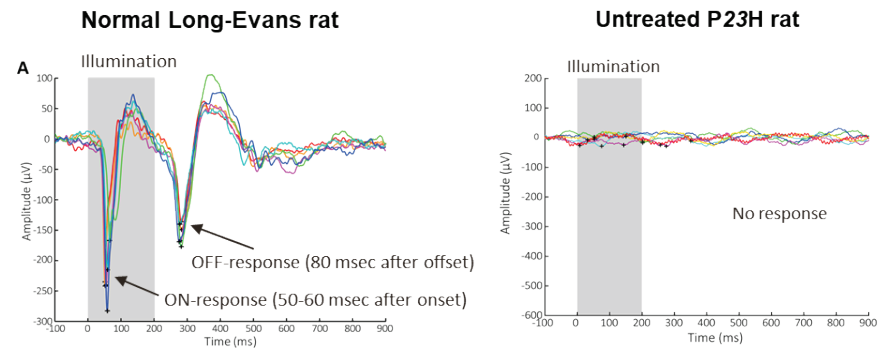
In vivo in NHP assessment 6 months after IVT injection



Restoration of a functional vision in P23H rats

Light-induced visual evoked cortical responses

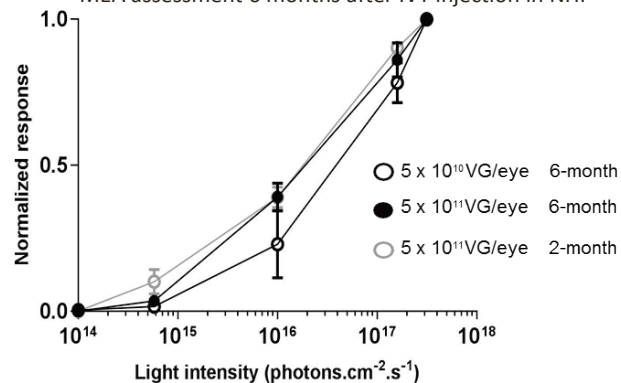
Full field 590 nm light from $\sim 4.7 \times 10^{15}$ to 1.1×10^{17} photons/cm²/sec



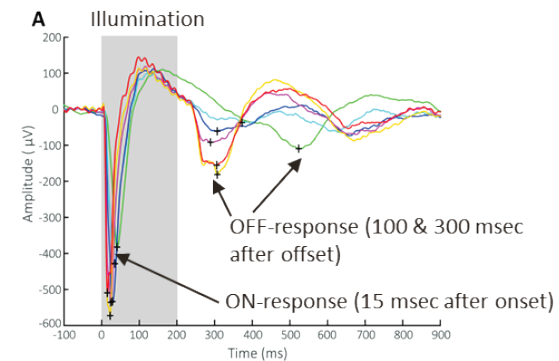
Dose-ranging response to firing relationship in NHP

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

MEA assessment 6 months after IVT injection in NHP



GS030-treated P23H rat



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 7.21×10^{10} VG/eye (low dose) vs 7.84×10^{11} VG/eye (high dose) in 100 μ L

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 7.84×10^9 VG/eye in 1 μ L; 590 nm LED light at 1.4×10^{16} vs 1.7×10^{17} photons/cm²/s vs ambient room light

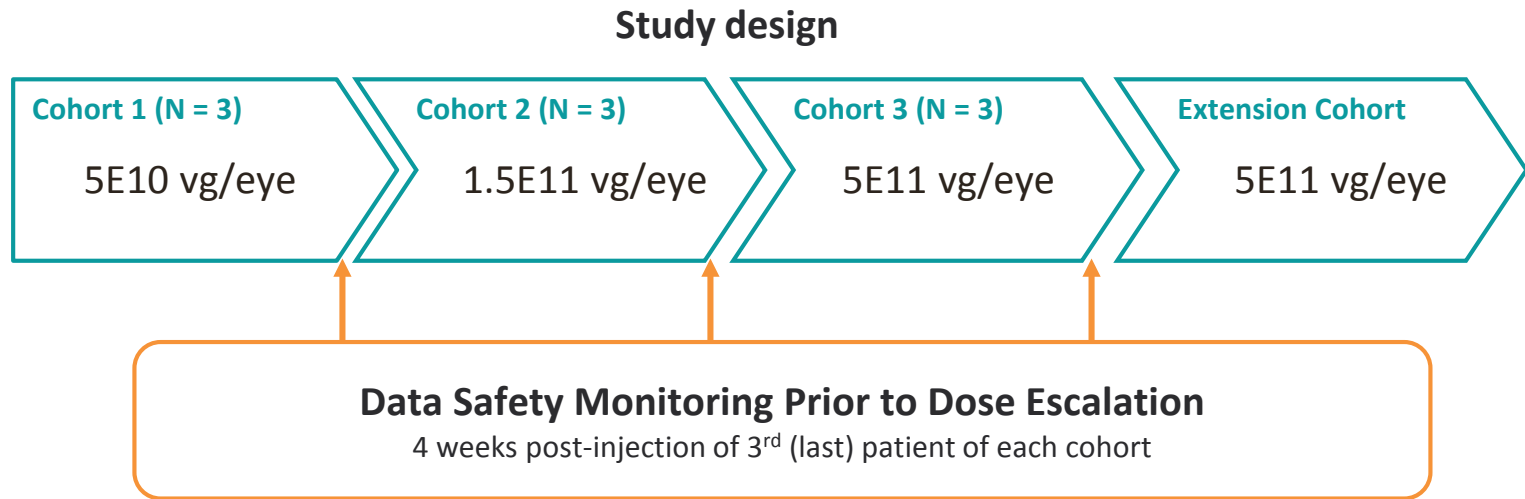
Local tolerance

- **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

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



- **First-in-man**, dose-escalation safety study, multi-center
- **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

**First patient treated in October 2018 at the Moorfields
Eye Hospital in the UK**

GS030: CMC progress & Regulatory interactions

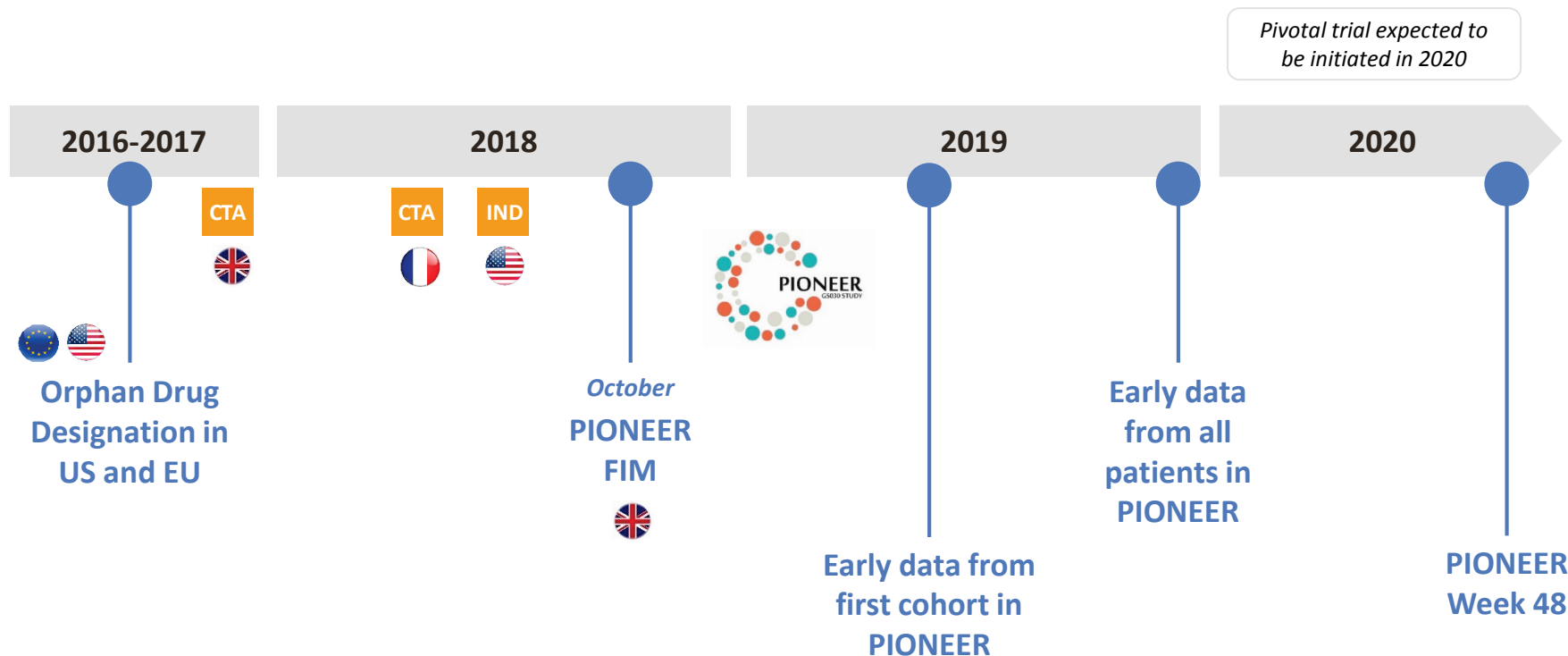
CMC

- **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 transferred 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**

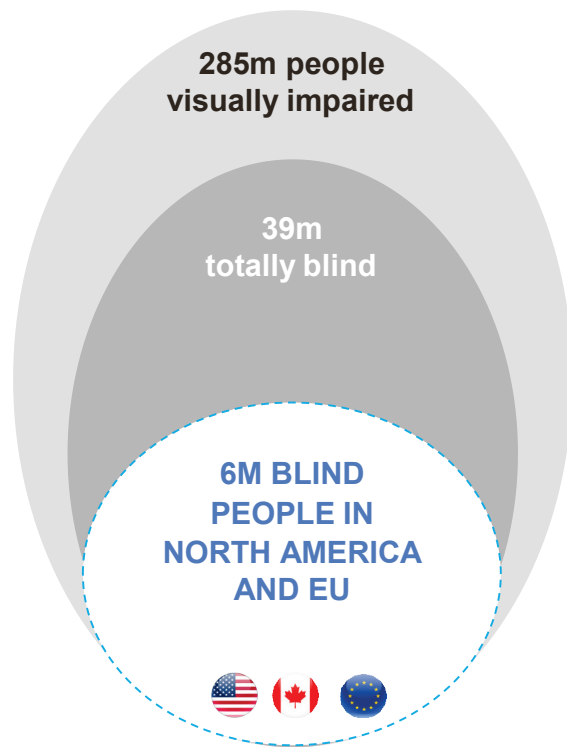
GS030 Key Milestones



Building high strategic value



Curing blindness represents major market opportunity

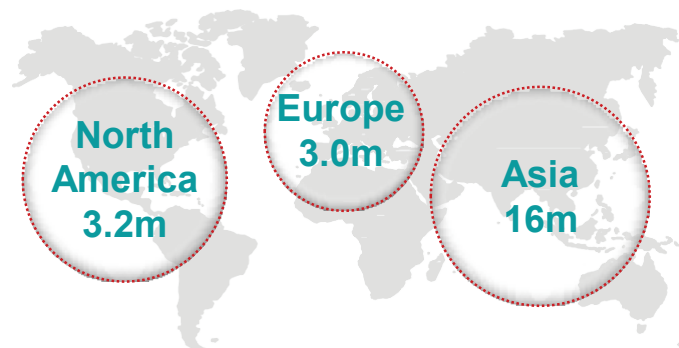


Source: WHO, IAPB-VISION2020, NORC-Univ. of Chicago / The Economic Burden of Vision Loss and Eye Disorders in the United States, 2014.

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



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



- 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

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



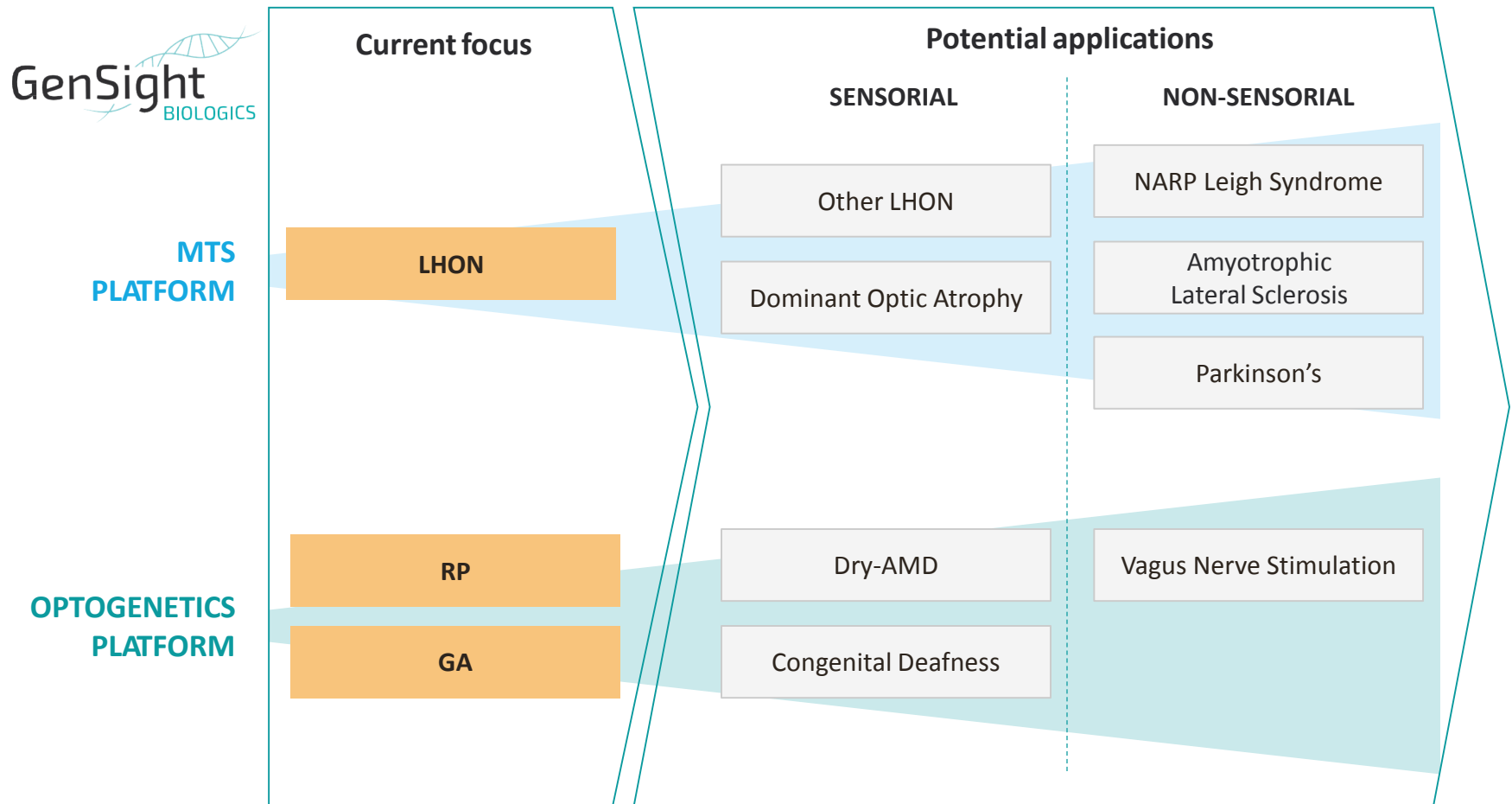
- Approved May 2016 for treatment of ADA-SCID
- List price: 594,000€ *per patient*
- Positive HTA assessments in UK and IT; covered by **EU Directive 2011/24***
 - Treatment administered only at the designated treatment center in Milan

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

- + 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.

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

Listed on Euronext Paris (SIGHT)

- Established in 2012, IPO in July 2016

Recognition from Blue-Chip specialist investors

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

Analyst coverage

- Oddo & Cie – Pierre Corby (FR)
- Gilbert Dupont – Jamila El Bougrini (FR)
- Chardan – Gbola Amusa (US)

Cash position

(as of Dec 31, 2018)

€26.2m

Number of outstanding shares

24.8m

Back-up Slides



REVERSE 72-week Topline Data

Visual Acuity improved by +15 and +12 ETDRS letter equivalent from BASELINE to Week 72 in GS010- and sham-treated eyes, respectively

LS Mean (SE) ^a	Change from BASELINE to Week 48	
	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	-0.218 (0.055)	+11
Sham Eyes	-0.211 (0.055)	+11

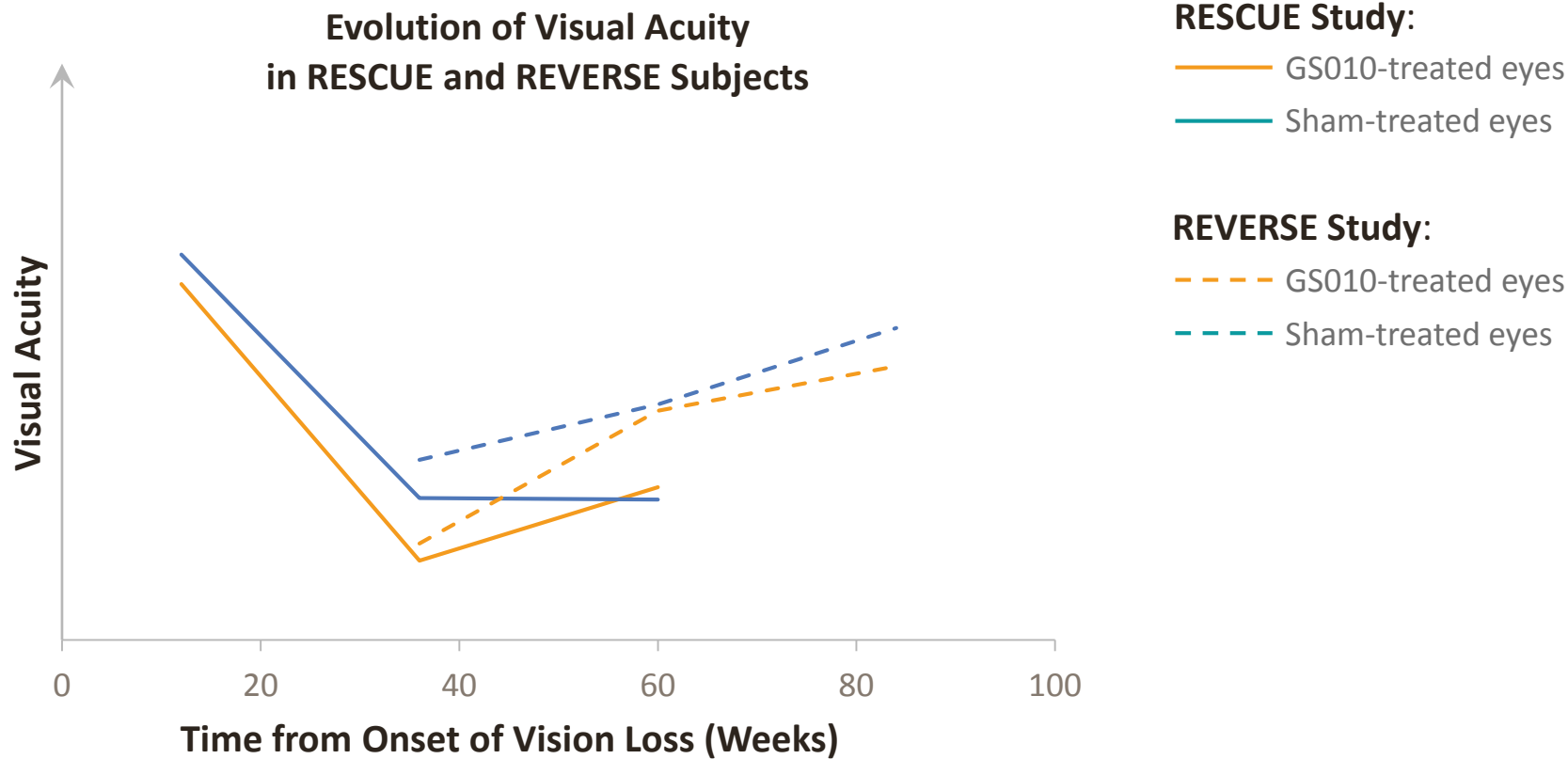
^a Primary Endpoint was assessed using a mixed model of analysis of covariance (ANCOVA) was used with change from baseline at week 48 as the response, and subject, eyes of the subject as random factor, treatment and the baseline LogMAR value as covariates in the model.

LS Mean (SE) ^a	Change from BASELINE to Week 72	
	LogMAR	ETDRS Letter Equivalent
GS010 Eyes	-0.294 (0.063)	+15
Sham Eyes	-0.246 (0.063)	+12

^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.

Broad coherence of RESCUE & REVERSE Topline Data

Visual acuity evolved bilaterally, with improvement seen once the disease passed a nadir point



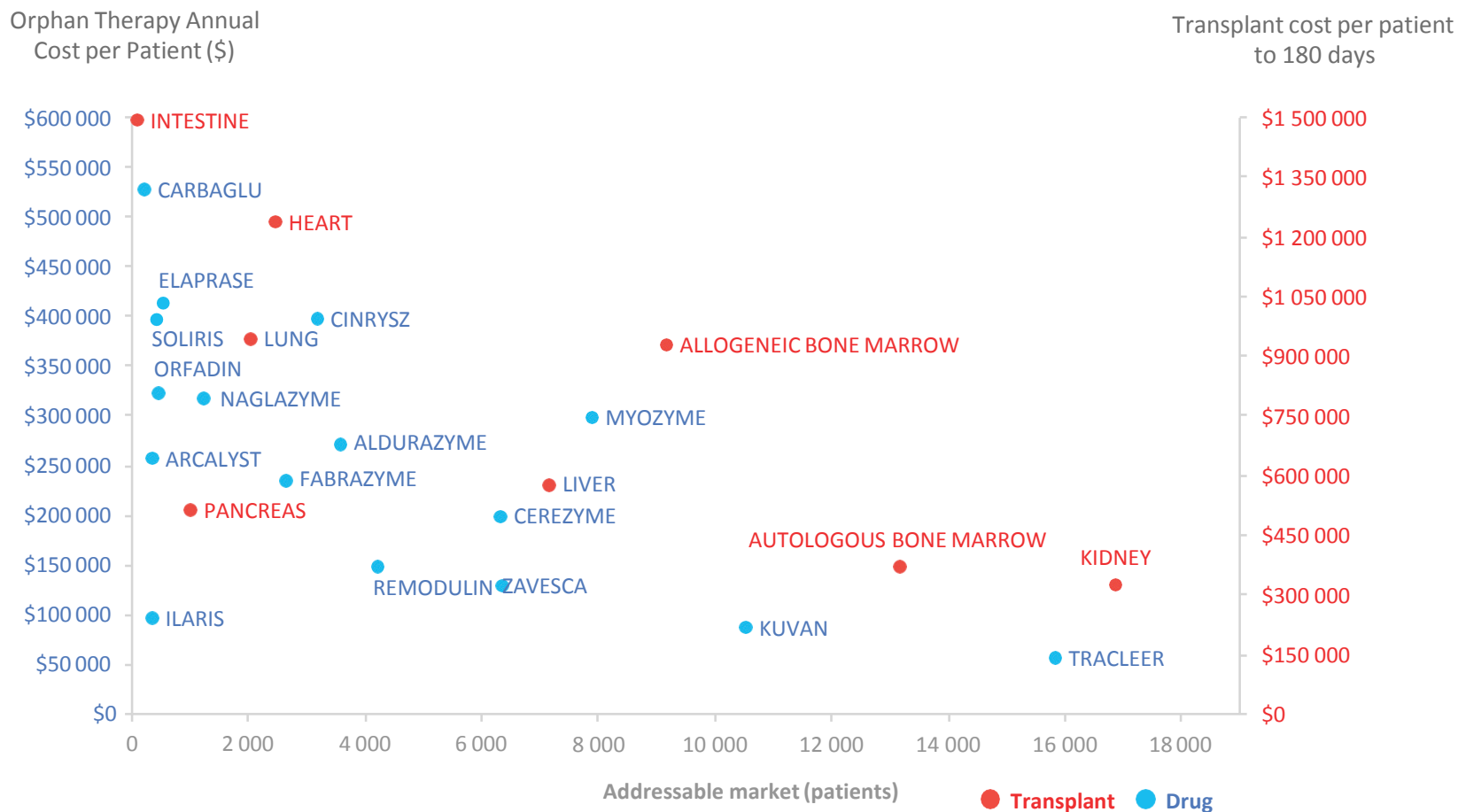
RESCUE 48-week Topline Data

Anatomic outcomes pointing to the right direction

- The difference between GS010-treated and sham-treated eyes in change from baseline of **temporal retinal nerve fiber layer** missed statistical significance ($p=0.0513$).
- The change from baseline in GS010-treated eyes of **papillo-macular bundle thickness** and **ganglion cell volume** was numerically superior to that in sham-treated eyes, though not statistically significant (p values > 0.05).

Anatomic measures showed similar trajectory for GS010-treated and sham-treated eyes, although not statistically significant at Week 48

Pricing and prevalence: organ transplant / gene therapy



Orphan therapies and transplants: a relevant pricing benchmark

Source: Nature Biotechnology, Volume 33, Number 9, September 2015: The payers' perspective on gene therapy.