GenSight BIOLOGICS

Corporate Presentation

January 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

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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)

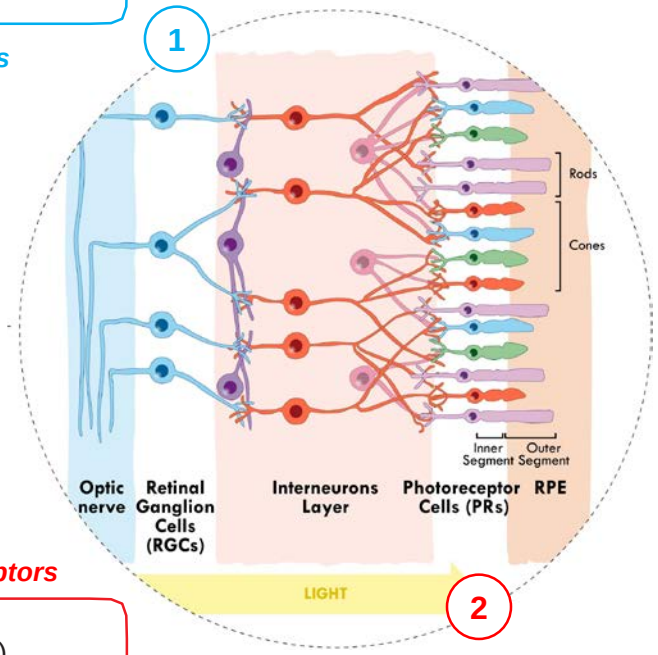
1. Degeneration of RGCs

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

*Except for exceptional circumstances for idebenone in Europe

Source: Company

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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 April 2018 **RESCUE**: Phase III top-line data expected in Q1 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 subject in ongoing Phase I/II clinical trial treated in October 2018 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

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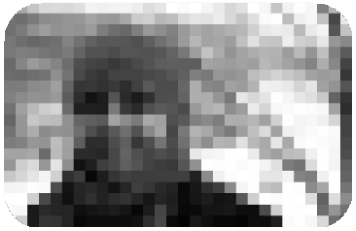
GS010

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



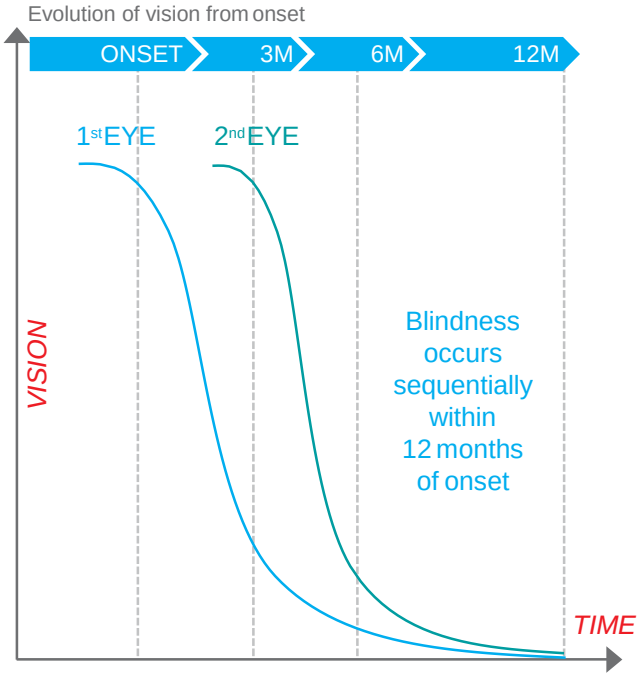


Image source: illustrated from Newamn NJ et al., Am J Ophthalmom. 141(6), 1061-1067,2006

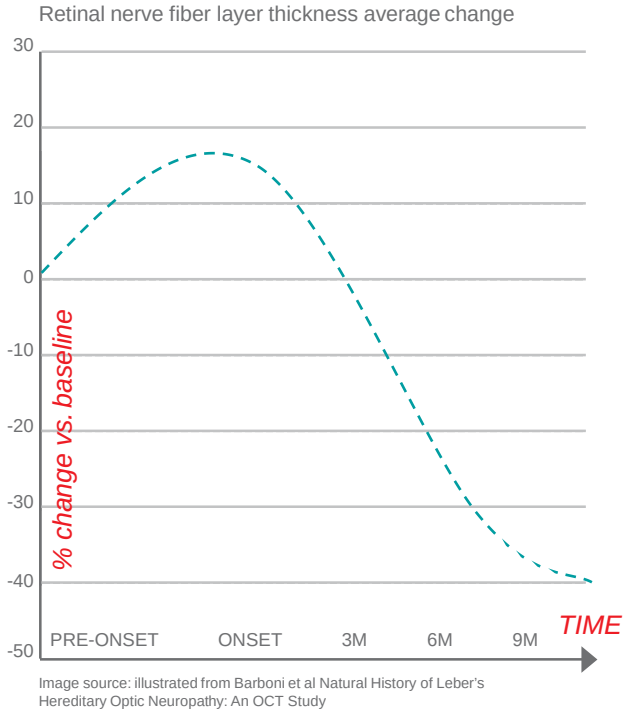


Image source: illustrated from Barboni et al Natural History of Leber's Hereditary Optic Neuropathy: An OCT Study

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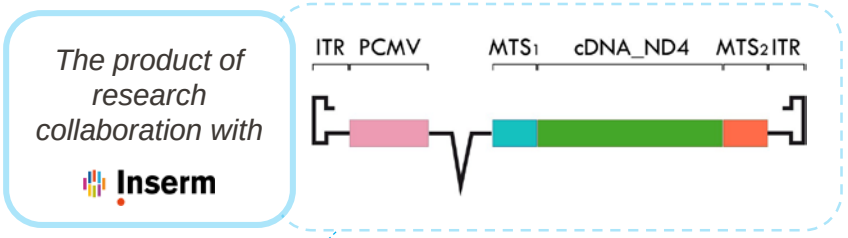
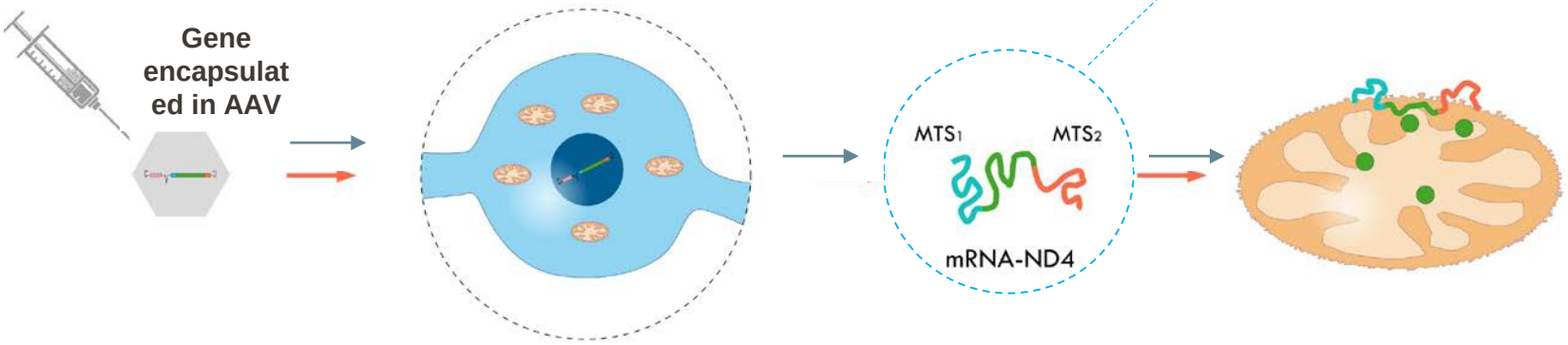
Solution: Gene therapy to produce working mRNA, with ***MTS* technology*** to shuttle mRNA directly to affected mitochondria

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

Source: Company

- 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

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REVERSE Data at 72 Weeks: **Favorable safety and tolerability profile**

- 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

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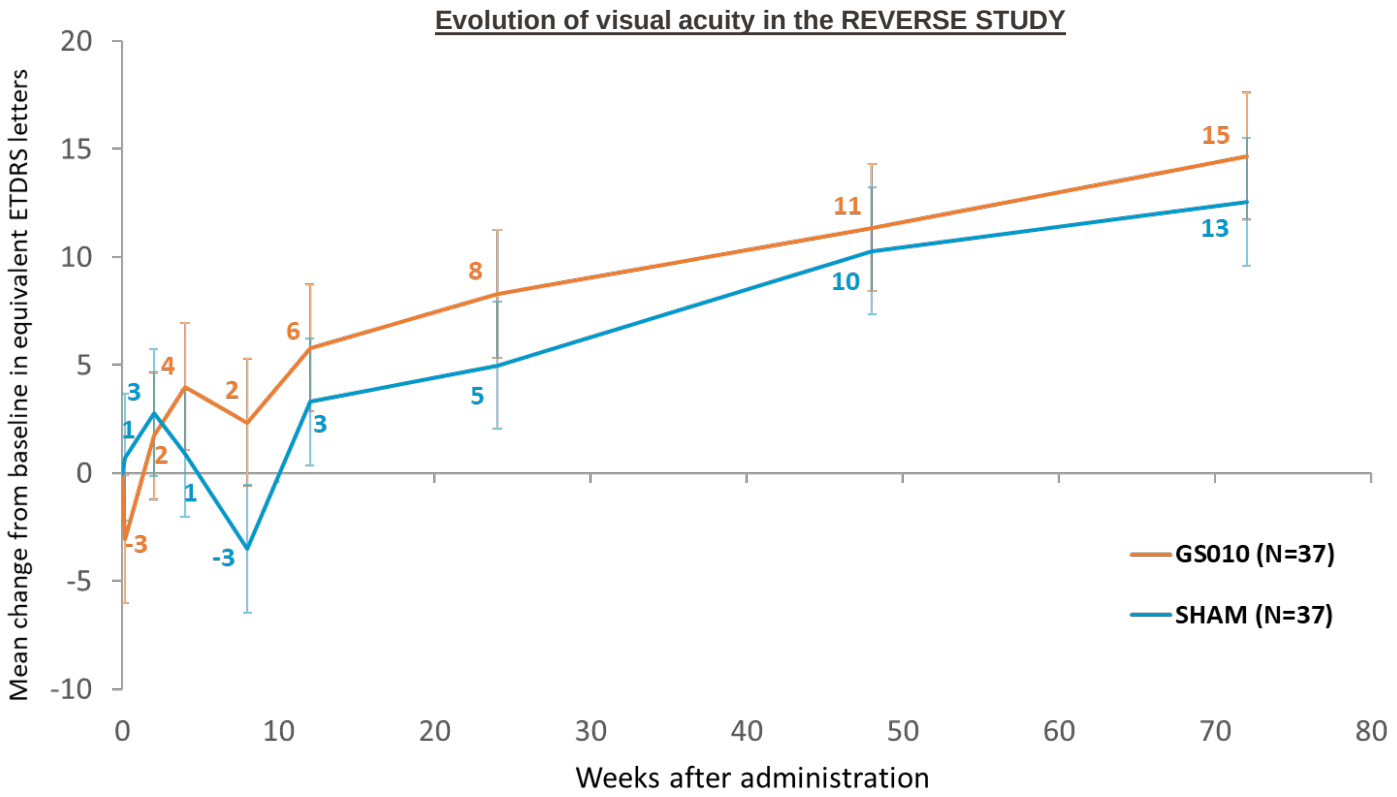
REVERSE Data at 72 Weeks: **Improvement of central Visual Acuity**

Clinically meaningful improvement of visual acuity

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



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REVERSE Data at 72 Weeks: **Improvement of Contrast Sensitivity**

Clinically meaningful 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

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

Preservation of the structure of the retina in drug-treated eyes

- SD-OCT demonstrated statistically significant preservation of retinal ganglion cells and preservation of retinal fiber layer in treated eyes vs. untreated eyes
  - **Change in retinal ganglion cell macular volume measured from baseline to week 72:**

    Treated eyes: no loss

    Untreated eyes: -0.044mm^3

    p=0.0060
  - **Change thickness of the temporal quadrant of the retinal nerve fiber layer from baseline to week 72:**

    Treated eyes: -1.6 µm

    Untreated eyes: -3.6 µm

    p=0.0521
- Sustained preservation of LHON-relevant retinal anatomy in drug-treated eyes further demonstrates the neuroprotective effect of GS010
- In a generalized estimating equation (GEE) model used to assess treatment effect on VA of ≧ 20/200 acuity, GS010-treated eyes were significantly more likely to achieve 20/200 endpoint than sham-treated eye

  p=0.0012

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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.

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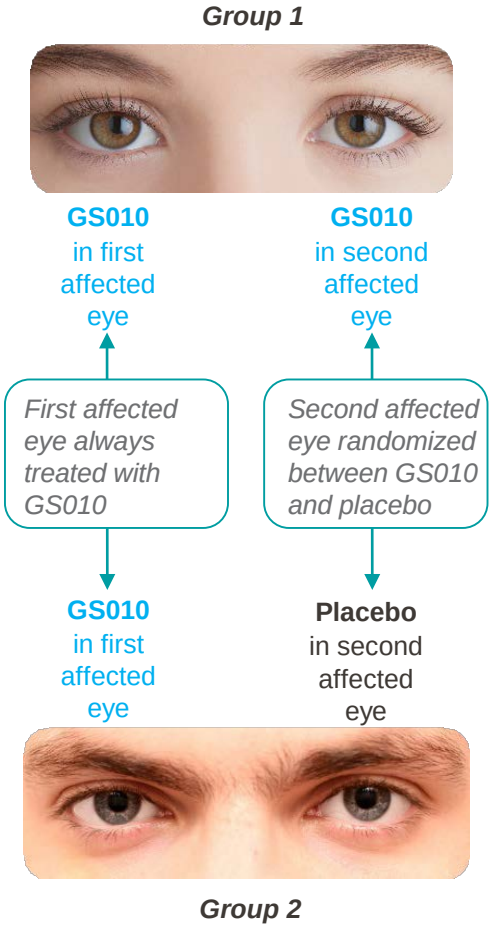
REFLECT Phase III trial: assess efficacy and safety of bilateral injection

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)

Design



Endpoints at Week 48

Primary

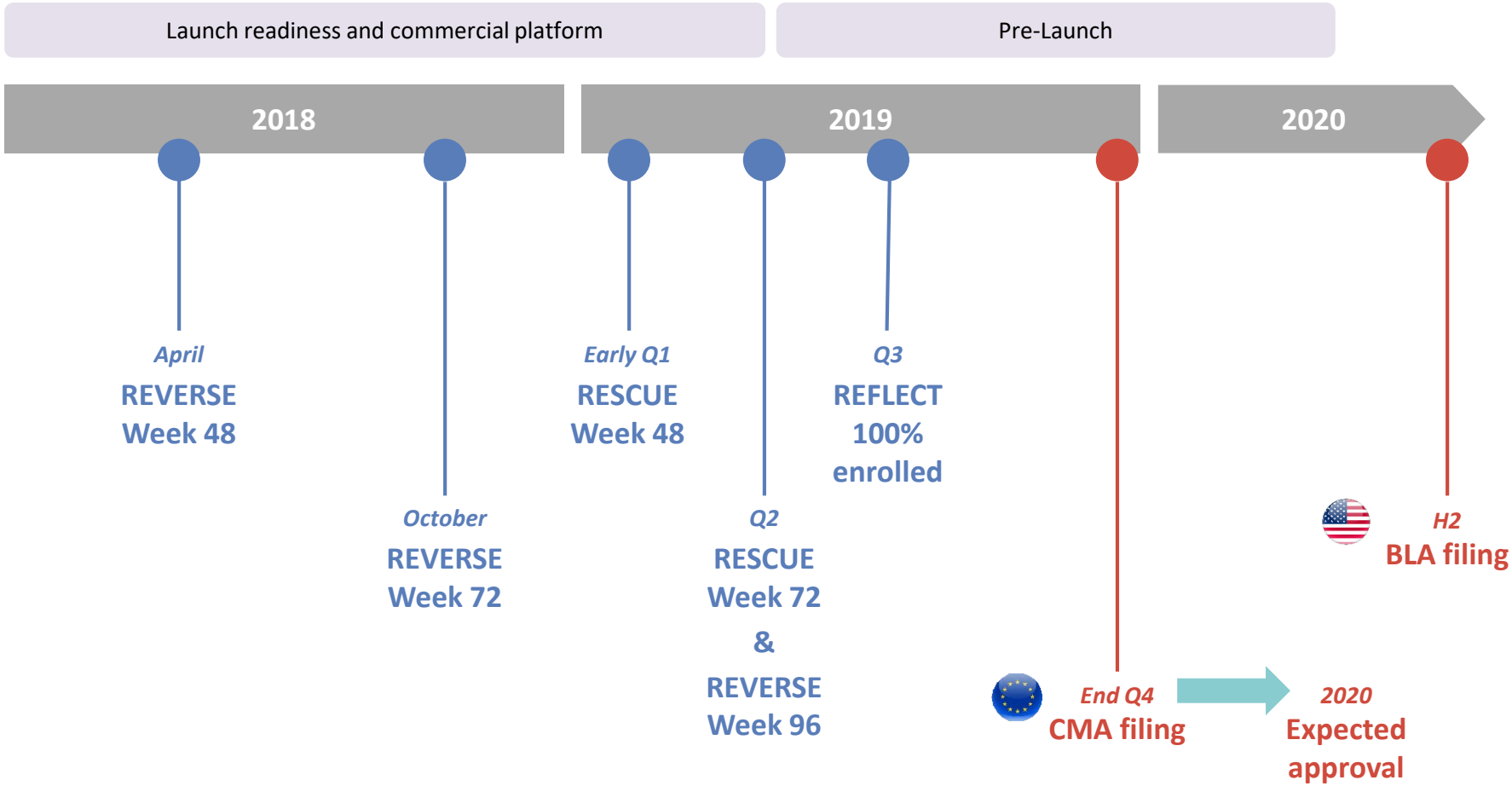
- Difference in change of vision compared to baseline between GS010 Treatment vs. Placebo in second affected/not yet affected eyes
  (LogMAR visual acuity used for statistical analysis)

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

GS010 Path to Market



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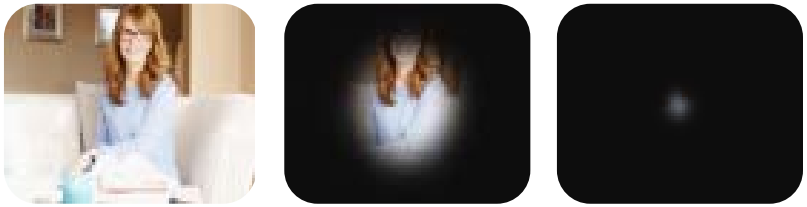
GS030

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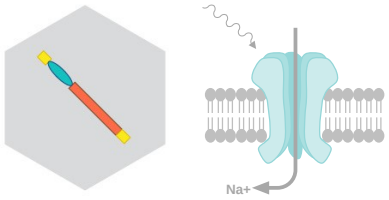
Optogenetics using GS030: gene therapy-based approach to restore light sensitivity

AAV2.7m8 + ChrimsonR

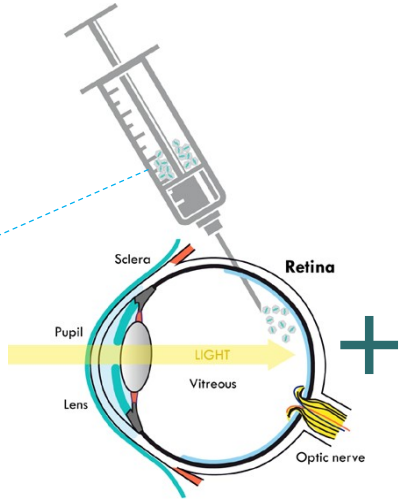


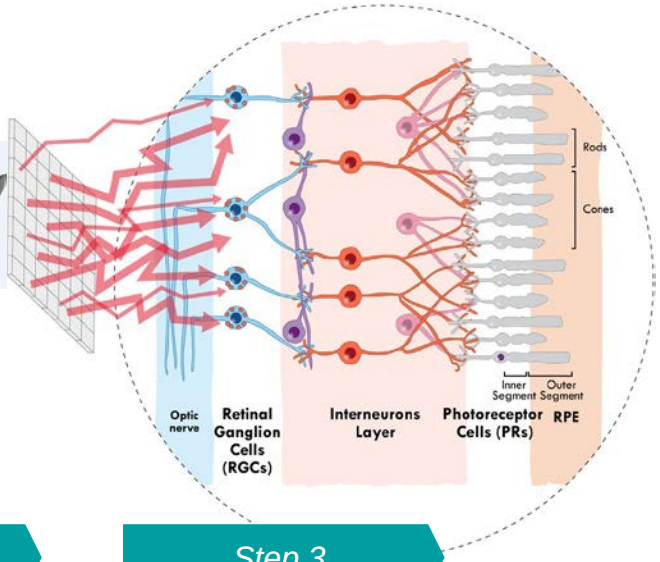
The product of research collaboration with

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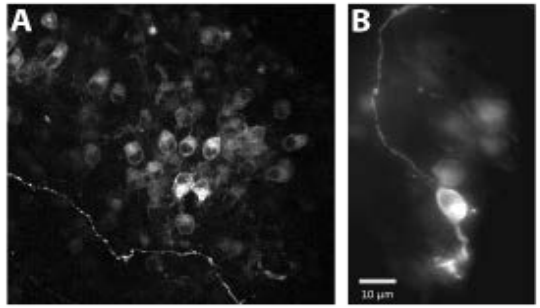
GS030: activated RGCs provide visual information to the higher visual centers

Localization of light-sensitive protein in NHP retina

Expression of ChrR-tdT in midget cells of monkey perifovea

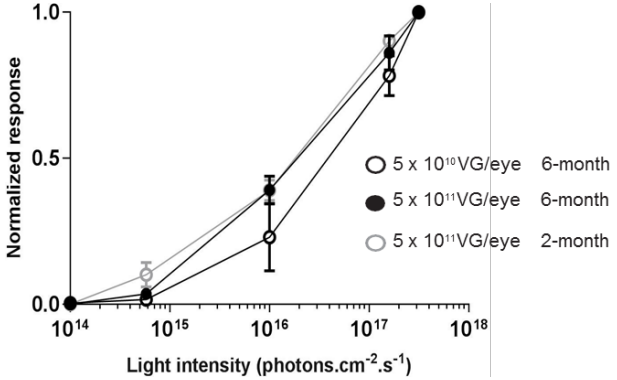
In vivo in NHP assessment 6 months after IVT injection



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

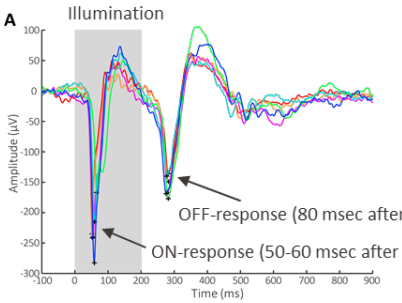


Restoration of a functional vision in P23H rats

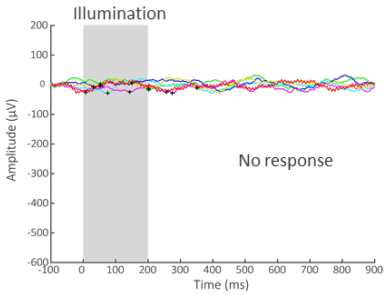
Light-induced visual evoked cortical responses

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

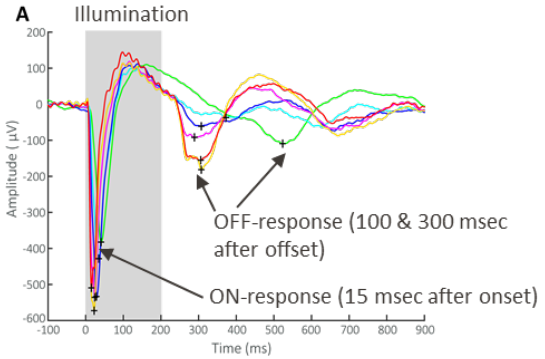
Normal Long-Evans rat



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 7.21×10^{10} VG/eye (low dose) vs 7.84×10^{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 7.84×10^{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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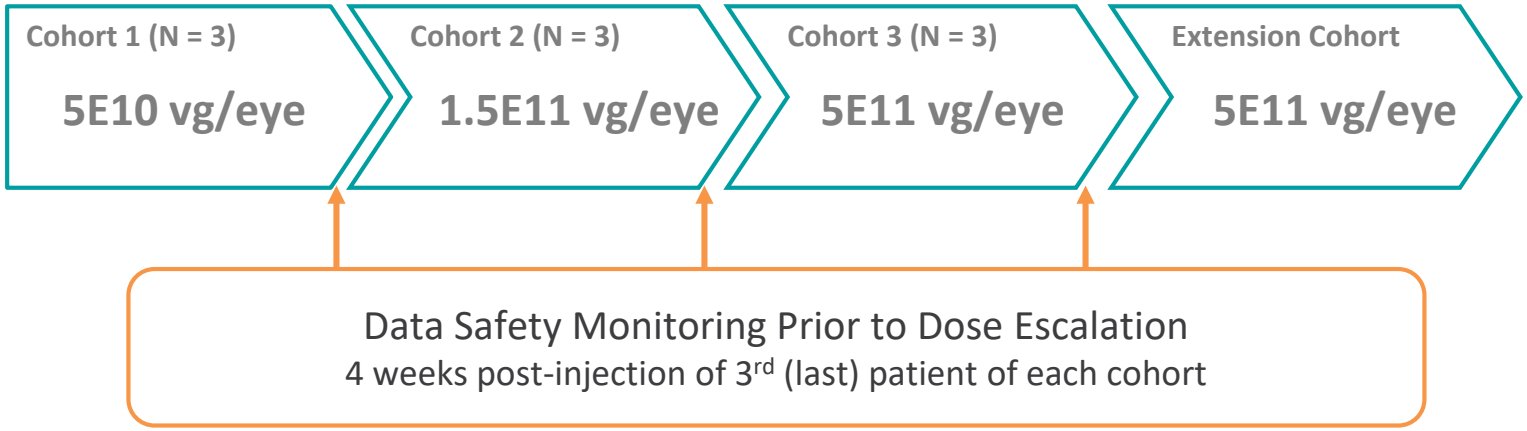
PIONEER Phase I/II clinical trial: A First-in-Man study

Study design



- **First-in-man**, dose-escalation safety study, multi-center
- **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 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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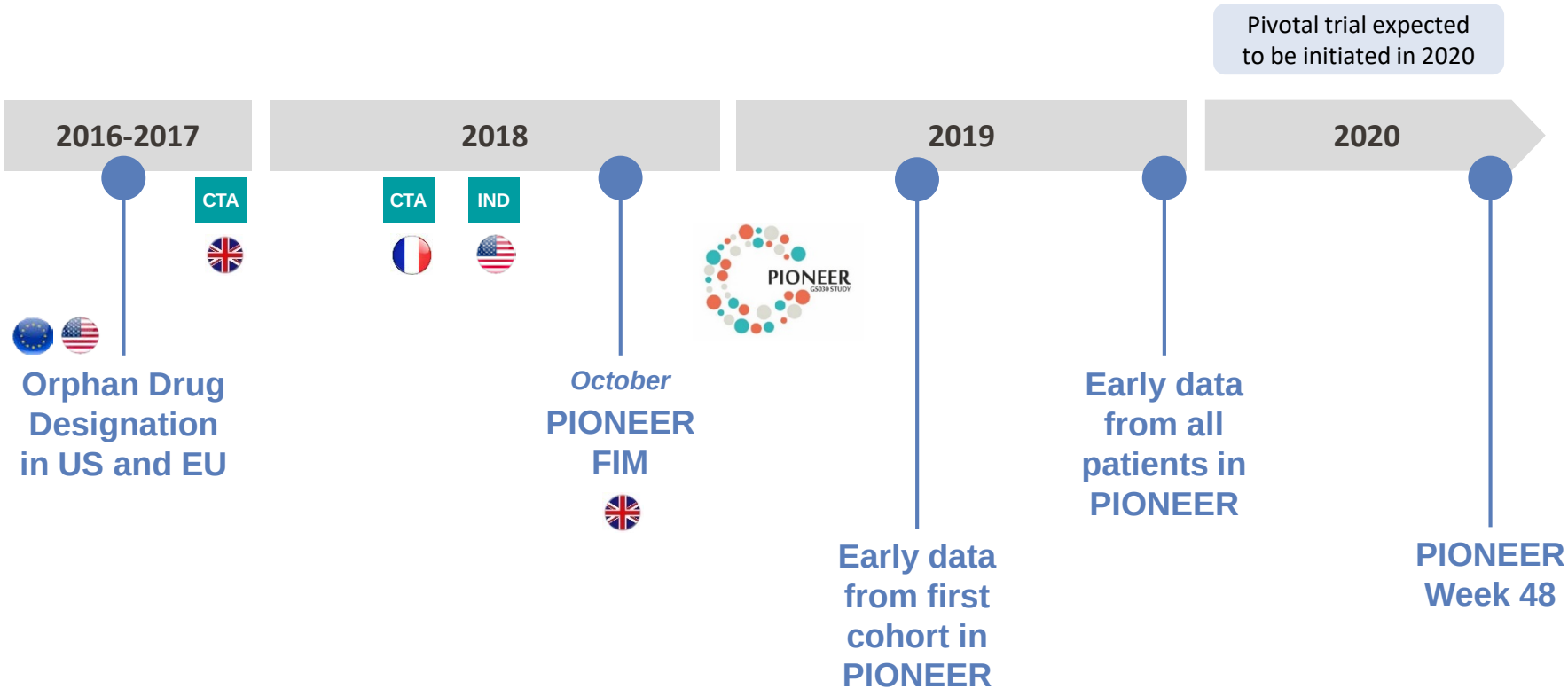
GS030 Key Milestones



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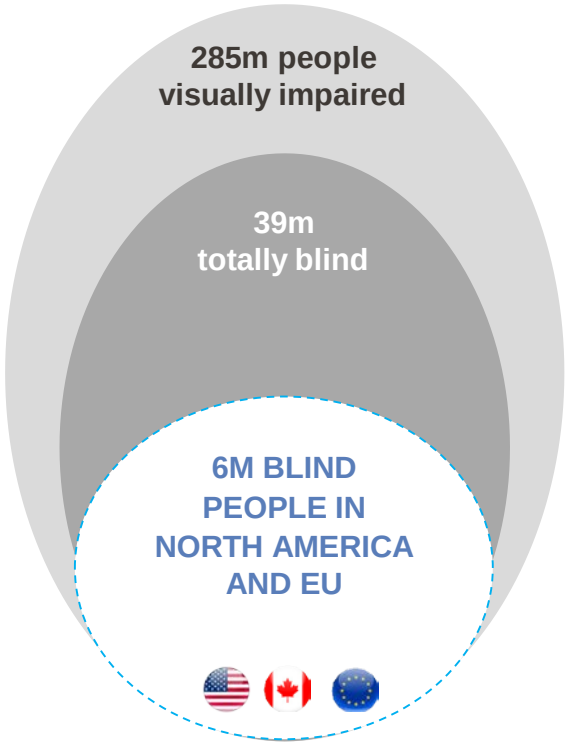
Building high strategic value

Curing blindness represents major market opportunity

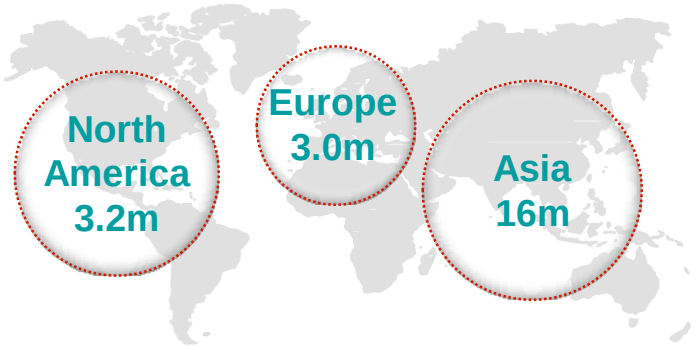


Source: WHO, IAPB-VISION2020, NORC-Univ. of Chicago / The Economic Burden of Vision Loss and Eye Disorders in the United States, 2014.

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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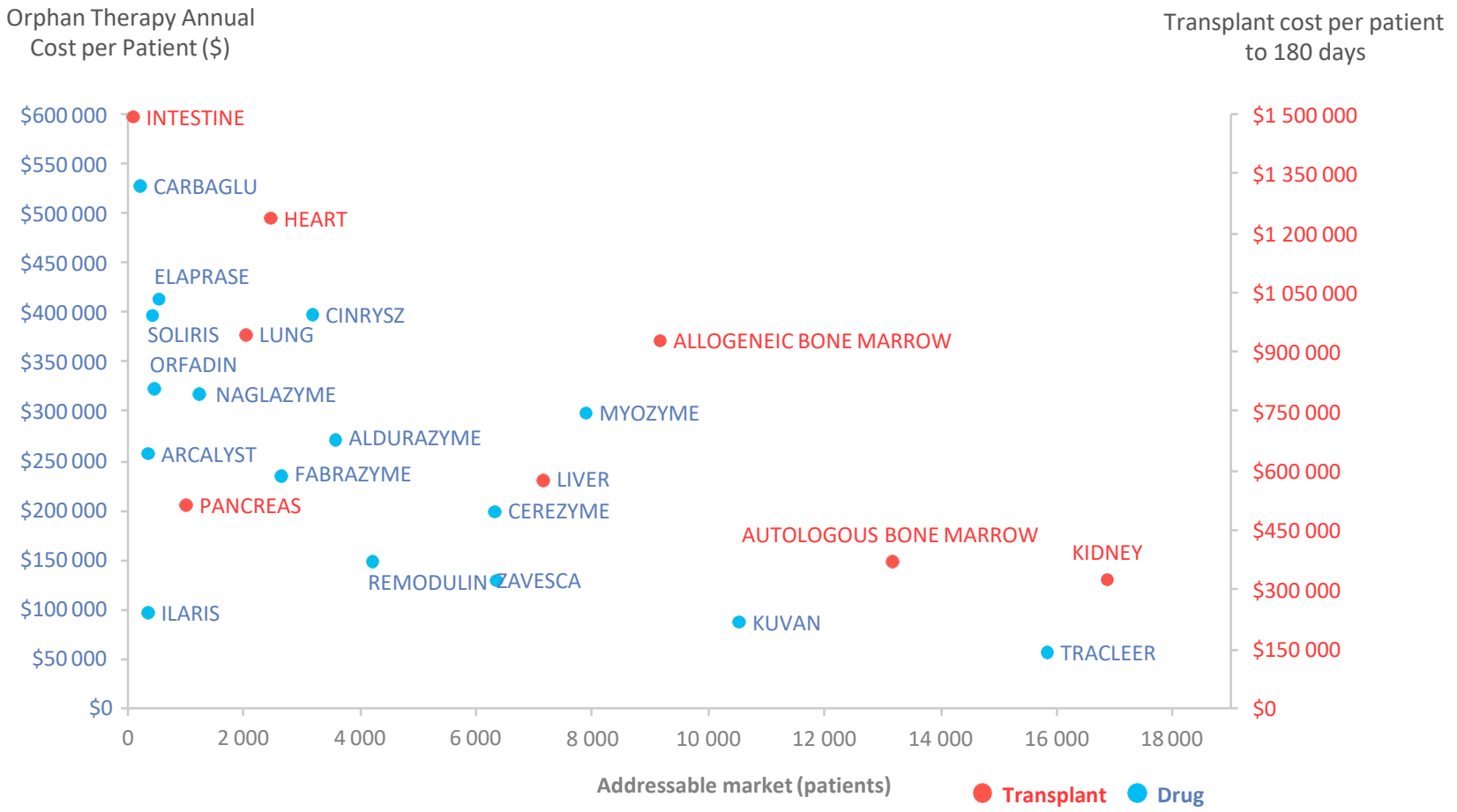
Pricing and prevalence: organ transplant / gene therapy

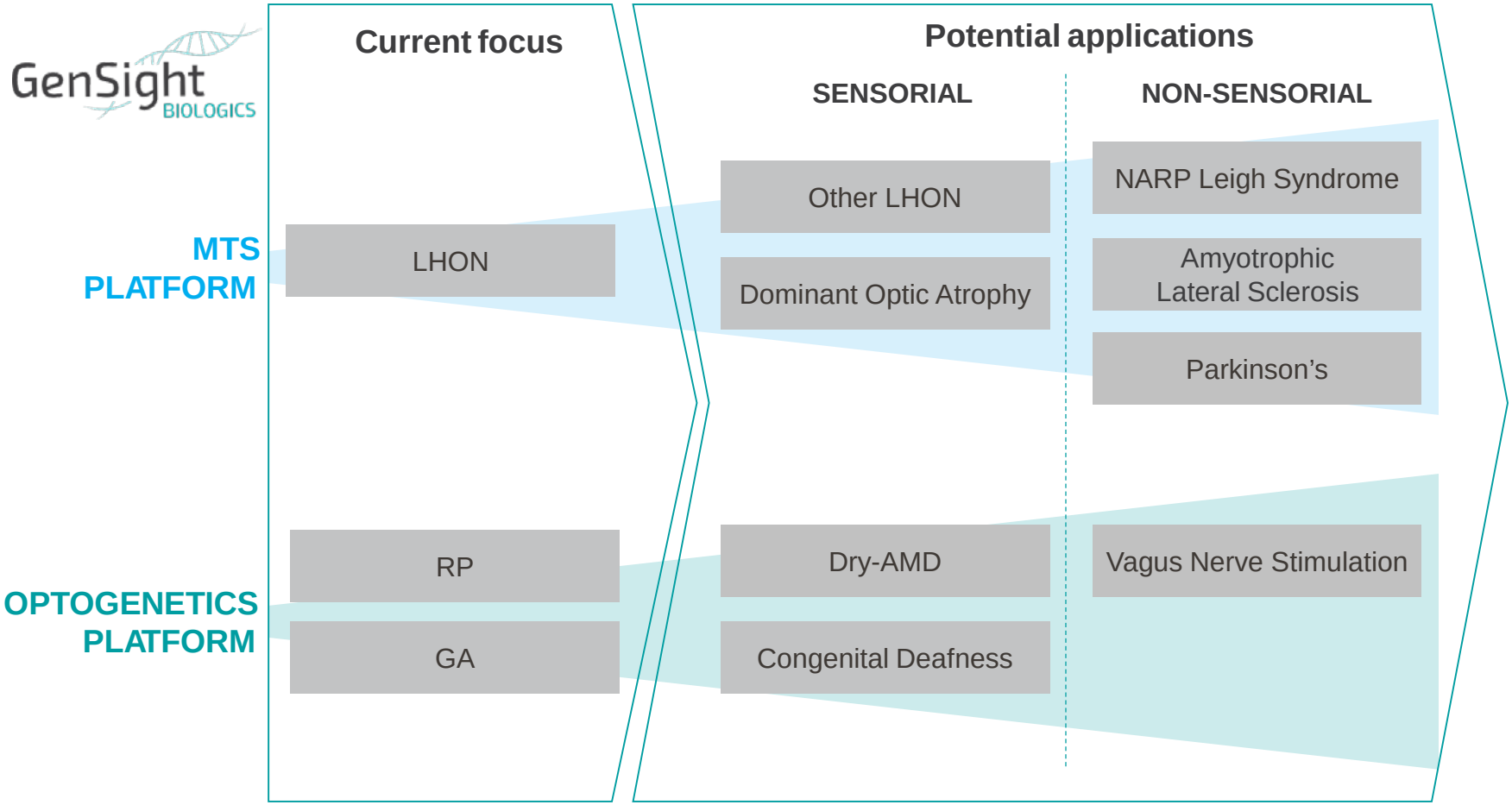


Orphan therapies and transplants: a relevant pricing benchmark

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

GenSight BIOLOGICS

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 Sep 30, 2018)

€39.2m

Number of outstanding shares

24.8m

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