Optogenetics in the Clinic:
PIONEER, a Phase 1/2a, Open-Label, Non-Randomized, Dose-Escalation Study to Evaluate Safety and Tolerability of GS030 in Subjects with Retinitis Pigmentosa

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Financial Disclosures

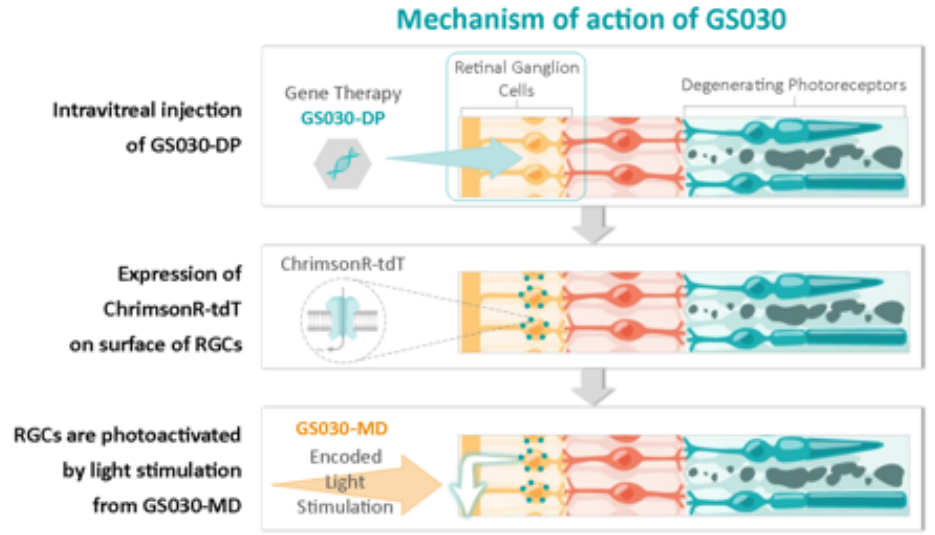
- FG, EV, DG, LB, and MT : employees of GenSight Biologics
- BR : chair of the scientific advisory board of GenSight Biologics and owns shares of Affinia Therapeutics and Arctos Medical AG
- JAS : personal financial interests in Pixium Vision, GenSight Biologics, Sparing Vision, Prophesee, and Chronolife
- EBS : consultant for GenSight Biologics
- DD : consultant for GenSight Biologics and inventor of a patented variant capsid adeno-associated virus and its use methods, with royalties paid to Adverum (WO2012145601 A2)
- SP : owns shares of, received consultant fees from, and has filled patents licensed to GenSight Biologics, has financial interests in Pixium Vision and Prophesee.

Summary of Presentation

Optogenetics to restore light sensitivity in blinding diseases

Retinitis pigmentosa

- Orphan genetic disease with +100 known mutations
- Sequential photoreceptor degeneration
- Slow and irreversible evolution leading to blindness



GS030: optogenetics to treat RP

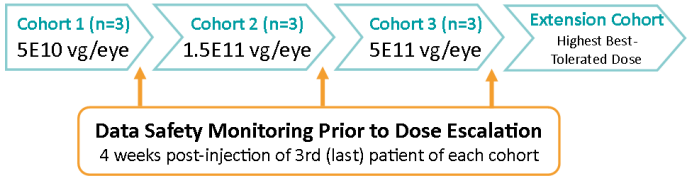
GS030 combines a gene therapy and a medical device to **confer light sensitivity to retinal ganglion cells**:

- **GS030-DP** is an AAV2.7m8 vector packing the ChrimsonR-tdT gene. ChrimsonR is a channelrhodopsin sensitive to orange light (550-600 nm).
  ⇒ This gene therapy is **independent of the causative mutation**
- **GS030-MD** is a light-stimulating device that encodes images of the visual field and projects them onto the retina at the appropriate intensity and wavelength to activate ChrimsonR.

Optogenetics in the clinic: the PIONEER study

PIONEER clinical trial

- Phase I/IIa **First-in-Man study**
- Study Population: end-stage non-syndromic RP
- Single intravitreal injection in the **worst-affected eye**
- Open label, non-randomized, dose-escalation study
- **Primary endpoint**: SAFETY and TOLERABILITY at Year 1 (Week 52)
- **Secondary endpoints**: functional vision, visual function, orientation and mobility, OCT, quality of life, immune response.
- **Training program**: Innovative platform and functional tests developed in collaboration with Streetlab to provide visual training to PIONEER patients.



Interim safety results at 1.5 years

- First two cohorts (n=6) were injected unilaterally with GS030-DP (5E10 and 1.5E11 vg/eye)
- Use of GS030-MD post-injection started 8 weeks later, at hospital under medical supervision
  ➢ Light stimulating glasses were **well tolerated**
- Most common ocular AEs were mild intraocular inflammation and mild light sensitivity started *before* therapeutic use of GS030-MD

Conclusions and next steps

- GS030 combined therapy is well tolerated so far
- 3rd cohort (highest dose of 5E11 vg/eye) should be injected in Q3 2020.

Retinitis pigmentosa

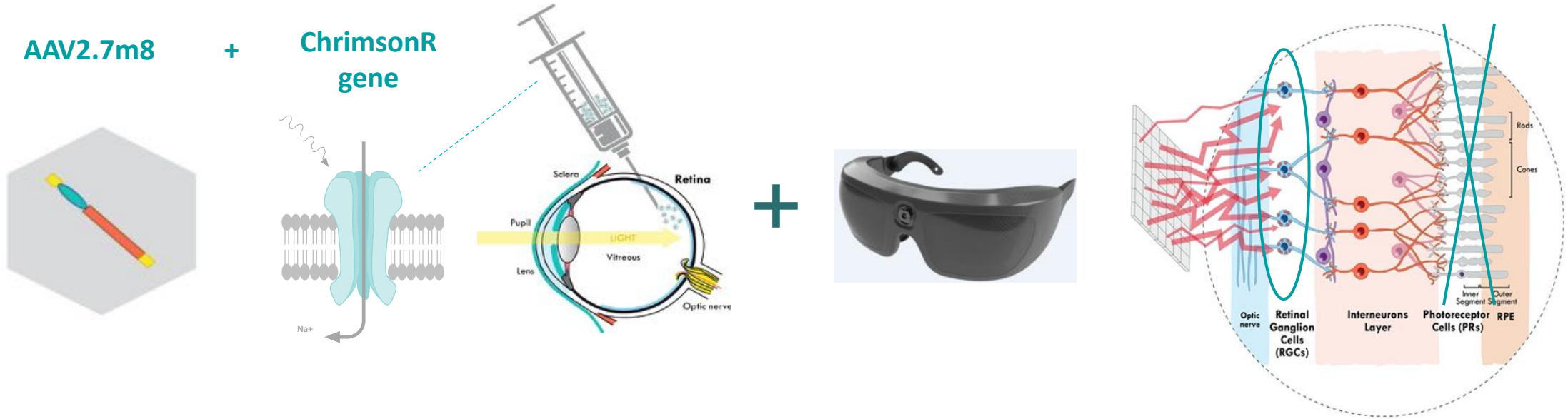
Retinitis Pigmentosa (RP)

- Genetic disease with +100 known mutations
- Sequential **photoreceptor degeneration**
- Irreversible evolution leading to blindness

Incidence	15K-20K / year
Prevalence	350K-400K (1.5 M worldwide)
Blindness Occurence	40-45 years old

GS030: optogenetics to treat RP

Combining gene therapy & medical device to confer light sensitivity to **retinal ganglion cells**:



- **GS030-DP** is an AAV2.7m8 vector packing the ChrimsonR-tdT gene.
  ChrimsonR is a channelrhodopsin sensitive to orange light (550-600 nm).
  ⇒ This gene therapy is **independent of the causative mutation**
- **GS030-MD** is a light-stimulating device that encodes images of the visual field and projects them onto the retina at the appropriate intensity and wavelength to activate ChrimsonR.

GS030: why is a photostimulating device needed?

1) To overcome the microbial opsin's low sensitivity to light

The microbial opsin ChrimsonR is unlikely to be activated by ambient light and cannot be activated by indoor lighting.

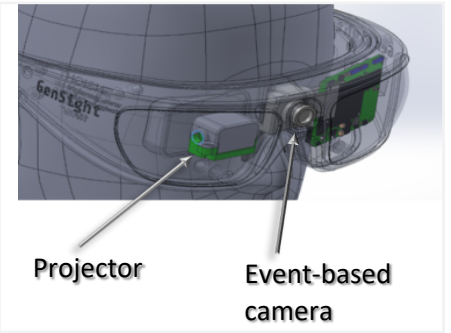
- An amplifying projection system sends a tailored light matching ChrimsonR optimal wavelength (580-610 nm).

GS030 MD

2) To mimic the natural visual pathway

The light amplifying device uses an event-based camera with 10^9 to 10^{16} photon.cm^{-2}.s^{-1} (143 dB) dynamic range in light intensity. It allows the capture of signals in low-light environments.

A specific **computation of the visual signal** mimics natural visual processing.

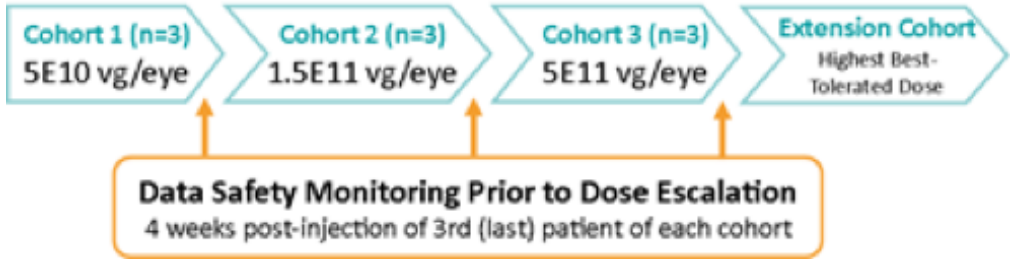


- GS030-MD delivers light stimulation at an **appropriate and constant irradiance level** regardless of environmental illumination.
- GS030-MD **encodes captured images** so that photostimulation signaling delivered to the RGCs **mimics natural visual processing**.

PIONEER: optogenetics in the clinic

PIONEER Clinical Trial

- Phase I/IIa **First-in-Man study** (NCT03326336)
- Study Population: end-stage non-syndromic RP
- Single intravitreal injection in the **worst-affected eye**
- Open label, non-randomized, dose-escalation study

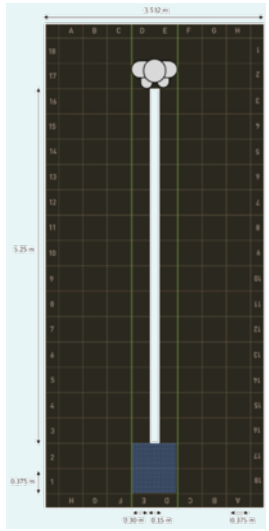


- **Primary endpoint**: SAFETY and TOLERABILITY at Year 1 (Week 52)
- **Secondary endpoints**: functional vision, visual function, orientation and mobility, OCT, quality of life, immune response.
- 3 investigational sites: Moorfields Eye Hospital (London, UK), Hôpital des XV-XX (Paris, France), UMPC Eye Center (Pittsburgh, USA).
- **Training program**: Innovative platform and functional tests developed in collaboration with Streetlab to provide visual training to PIONEER patients.
  - ➢ Help them understand the visual perceptions provided by GS030 and learn how to use their new vision

Two-part visual training before home use: Practical exercises and functional tests

streetlab avec l'Institut de la Vision

PIONEER functional endpoints: orientation and mobility



Line task:

- The platform is covered in matt black flooring lined with a grid and a 15-cm wide white line
- Patient is instructed to follow the white line and stop when they think they have reached the end (blue zone)
- After 3 minutes, the test is stopped whether or not the subject has reached the end

Door task:

- A mock door is placed on the wall
- Patient is instructed to find the mock door and touch it
- After 3 minutes, the test is stopped whether or not the subject has reached the door

Tests are performed with and without GS030-MD

PIONEER: interim safety results at 1.5 years

- First two cohorts (n=6) were injected unilaterally with GS030-DP (5E10 and 1.5E11 vg/eye)
- Use of GS030-MD post-injection started 8 weeks later, at hospital under medical supervision
  - ➢ Light stimulating glasses were **well tolerated**
- Good safety profile up to 1.5 years after IVT:
  - No serious adverse events, no study discontinuations
  - Most common ocular AEs were:
    - mild intraocular inflammation responsive to corticosteroid treatment
    - mild light sensitivity started before therapeutic use of GS030-MD

Conclusions and next steps:

- GS030 combined therapy is well tolerated so far
- On March 25, 2020, Data Safety Monitoring Board approved dose escalation in 3rd cohort (highest dose of 5E11 vg/eye).
- Injection of first patient of cohort 3 planned in July 2020