

GenSight Biologics Announces *Nature Medicine* Case Report Showing Visual Recovery after GS030 Optogenetic Treatment

- First peer-reviewed publication to document partial visual recovery in a blind patient with late-stage inherited retinal disease
- GS030 treatment combining gene therapy with light-stimulating medical device enabled patient with 40-year history of retinitis pigmentosa to regain ability to perceive, locate, count and touch objects
- Electroencephalographic (EEG) readings during visual tests suggest task-related activity in the visual cortex
- Video showing patient successfully performing visual tests available on www.gensight-biologics.com

Paris, France, May 25, 2021, 7:30 am CEST – GenSight Biologics (Euronext: SIGHT, ISIN: FR0013183985, PEA-PME eligible), a biopharma company focused on developing and commercializing innovative gene therapies for retinal neurodegenerative diseases and central nervous system disorders, today announced that the highly-regarded journal *Nature Medicine* has published the first case report of partial recovery of visual function in a blind patient with late stage retinitis pigmentosa (RP). The subject is a participant in the ongoing PIONEER Phase I/II clinical trial of GenSight Biologics' GS030 optogenetic therapy. Published in the May issue under the title "**Partial recovery of visual function in a blind patient after optogenetic therapy**", the paper* is the first peer-reviewed documentation of visual recovery after a blind patient was treated with optogenetic therapy.

"These are truly groundbreaking findings that move the promise of optogenetics another step from therapeutic concept to clinical use," commented **Bernard Gilly**, Co-Founder and Chief Executive Officer of GenSight. *"These could not have occurred without the close collaboration we enjoyed with our partners at the Institut de la Vision, the Institute of Ophthalmology Basel and Streetlab. We are especially grateful to the patients who are participating in our trial, whose experiences and input will help us design the next stage of GS030's clinical development. We will now accelerate the GS030 program to make it our second product to reach the market after LUMEVOQ."*

Optogenetic therapies combine cellular expression of light-sensitive opsins with light stimulation using a medical device. GS030 uses an optimized viral vector (GS030-DP) to express the light-sensitive opsin ChrimsonR in retinal ganglion cells and proprietary light-stimulating goggles (GS030-MD) to project the right wavelength and intensity of light onto the treated retina. GS030-DP is administered via an intravitreal injection.

"It was breathtaking to witness the first recovery of some visual function in a blind patient," commented **Dr. Botond Roska, MD, PhD**, last and co-corresponding author and a pioneer in the field of optogenetic vision restoration. Dr. Roska is Founding Director of the Institute of Molecular and Clinical Ophthalmology Basel (IOB) in Switzerland and a Co-Founder of GenSight. *"We have worked on optogenetic therapy in the lab for 16 years and now seeing the proof of concept in a patient is a unique experience,"* he said. *"I am most*

grateful to have shared this long journey with José Sahel, a fellow founder of GenSight; the dedicated team at GenSight; and our other collaborators.”

The subject in the case report, who had been diagnosed with RP 40 years prior to enrollment, had such low visual acuity that prior to receiving GS030, he could only perceive light. His gene therapy injection was followed four and a half months later by training on the use of the GS030-MD device. Seven months after the start of his training, he began to report signs of visual improvement. Visual function tests showed he acquired the ability to perceive, locate, count and touch objects when his treated eye was stimulated with the GS030-MD goggles. Without the goggles, he could not perform the tasks.

While the patient performed vision-oriented tasks, recordings were taken using extracranial multi-channel electroencephalography (EEG), a non-invasive technique that provides a readout of neuronal activity across the cortex. The EEG signals suggest that the act of carrying out the visual perception tests was accompanied by neurophysiological activity in the visual cortex.

In addition, the patient also reported significant improvements in his ability to conduct day-to-day activities such as navigating in outdoor and indoor environments and detecting household objects and furniture.

“Watching a patient benefit for the first time from this trial using optogenetics to treat blindness has been a uniquely rewarding experience,” commented **Dr. José-Alain Sahel, MD, PhD**, lead and co-corresponding author, Co-Founder of GenSight, and Founder of the *Institut de la Vision* (Sorbonne-Université/Inserm/CNRS), Paris, France. Dr. Sahel is also Director of Institut Hospitalo-Universitaire FOrE-SIGHT, Paris, France, and Distinguished Professor and Chairman of the Department of Ophthalmology at the University of Pittsburgh School of Medicine and UPMC (University of Pittsburgh Medical Center), USA. He added, *“Being able to take part in bringing this new scientific approach to the clinic reflects the long-term collaboration with Botond Roska, the scientists of the Vision Institute, our clinicians, the Streetlab and psychophysics teams, and GenSight.”*

A video of the patient performing the tests, which was submitted as supplementary material to *Nature Medicine*, can be viewed at www.gensight-biologics.com.

Key Opinion Leader Webcast: June 4, 2021 at 2:00 PM CEST/8:00 AM EDT

Dr. Sahel and Dr. Roska will discuss the case report on a KOL webcast dedicated to Optogenetics and GS030 and hosted by GenSight Biologics.

Details will be announced at a later date.

Context

RP is the leading cause of inherited blindness and is caused by mutations in more than 71 different genes.^a By using gene therapy to induce light sensitivity in unaffected retinal ganglion cells, GS030 overcomes the challenge among genetics-based treatments of exclusively addressing a specific underlying mutation and thus offers a treatment that is independent of the underlying pathogenic mutation.

PIONEER is the Phase I/II first-in-human, multi-center, open-label dose-escalation clinical trial to evaluate the safety and tolerability of GS030 in subjects with late-stage RP. A total of 12 to 18 subjects are planned to be enrolled. Three cohorts with three subjects each will be administered an increasing dose of GS030-DP via a single intravitreal injection in their worse-seeing eye. An extension cohort will receive the highest tolerated dose. A Data Safety Monitoring Board (DSMB) reviews the safety data of all treated subjects in each cohort and makes recommendations before the next cohort is enrolled. The primary outcome analysis will be the safety and tolerability at one year post-injection.

In line with the PIONEER protocol, the subject received the lowest dose ($5.0E10$ vector genomes) of GS030-DP in his worse-seeing eye. Four and a half months after injection, the patient began systematic training at Streetlab, a specialized visual rehabilitation facility, to learn how to use the light-stimulating goggles. The timing of the training was based on the estimated time it takes for the expression of light-sensitive opsin to stabilize in foveal ganglion cells.

Highlights of Visual Function Findings from Case Report

In the first visual test, the subject was asked to perceive, locate, and touch a single object placed in front of him on a white table. The subject had no success without the goggles. When the subject's treated eye was stimulated by the GS030-MD goggles, his ability to perceive, locate, and touch an object depended on the size of the object, with a significantly higher rate of successful trials with a large object (a notebook; 92%) than with the smaller object (a staple box; 36%). The success rate was similar for objects at different contrasts, suggesting that even objects at lower contrasts generated enough retinal activity for perception. Finally, the success rate was similar for the different tasks of perceiving, locating, and touching, suggesting that once the object was perceived, the patient could coordinate his motor system with the percept.

The second visual test required the subject to perceive, count, and locate two or three tumblers of different contrasts placed in front of him on a white table. As in the first test, the subject had no success without the goggles. When the subject's treated eye was stimulated by the GS030-MD goggles, the patient perceived, correctly counted, and located the objects in the majority (58-63%) of the trials. As in the first test, the success rate was similar for objects of different contrasts.

In the third visual test, the patient had to assess the presence or absence of a tumbler on a white table. The success rate with the goggles stimulating the treated eyes was statistically significantly higher than without the goggles (41% vs. 6%; $p < 0.001$).

Highlights of Safety Findings from Case Report

In-depth ocular examinations were performed regularly before and after injection, and potential intraocular inflammation was monitored according to international guidelines of the Standardization of Uveitis Nomenclature (SUN) Working Group.^b Both eyes of the subject showed no intraocular inflammation and no changes in the anatomy of the retina; there were no ocular or systemic adverse events over the 84 weeks of assessment.

The subject tested the light-stimulating goggles three times before being injected with the gene therapy. On each of these occasions, he reported no change of vision or photophobia.

Detailed findings can be found at <https://www.nature.com/articles/s41591-021-01351-4>.

*About the paper:

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

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About GenSight Biologics

GenSight Biologics S.A. is a clinical-stage biopharma company focused on developing and commercializing innovative gene therapies for retinal neurodegenerative diseases and central nervous system disorders. GenSight Biologics' pipeline leverages two core technology platforms, the Mitochondrial Targeting Sequence (MTS) and optogenetics, to help preserve or restore vision in patients suffering from blinding retinal diseases. GenSight Biologics' lead product candidate, LUMEVOQ® (GS010; lenadogene nolparvovec), has been submitted for marketing approval in Europe for the treatment of Leber Hereditary Optic Neuropathy (LHON), a rare mitochondrial disease affecting primarily teens and young adults that leads to irreversible blindness. Using its gene therapy-based approach, GenSight Biologics' product candidates are designed to be administered in a single treatment to each eye by intravitreal injection to offer patients a sustainable functional visual recovery.

About GS030

GS030 leverages GenSight Biologics' optogenetics technology platform, a novel approach to restore vision in blind patients using a combination of ocular gene therapy and tailored light-activation of treated retinal cells. The gene therapy, which is delivered via a single intravitreal injection, introduces a gene encoding for a light-sensitive protein (ChrimsonR-tdT) into retinal ganglion cells, making them responsive to light and bypassing photoreceptors killed off by diseases such as retinitis pigmentosa (RP). Because ChrimsonR-tdT is activated by high intensities of amber light, a wearable medical device is needed to stimulate the treated retina. The optronic light-stimulating goggles (GS030-MD) encode the visual scene in real-time and project a light beam with a specific wavelength and intensity onto the treated retina. Treatment with GS030 requires patients to wear the external wearable device in order to enable restoration of their visual function. With the support of the *Institut de la Vision* in Paris and the team of Dr. Botond Roska at the Friedrich Miescher Institute in Basel, GenSight is investigating GS030 as therapy to restore vision in patients suffering from late-stage RP. GenSight's optogenetics approach is independent of the specific genetic mutations causing blindness and has potential applications in other diseases of the retina in which photoreceptors

degenerate, like dry age-related macular degeneration (dry-AMD). GS030 has been granted Orphan Drug Designation in the United States and Europe.

About Optogenetics

Optogenetics is a biological technique that involves the transfer of a gene encoding for a light sensitive protein to cause neuronal cells to respond to light stimulation. As a neuromodulation method, it can be used to modify or control the activities of individual neurons in living tissue and even in-vivo, with a very high spatial and temporal resolution. Optogenetics combines (1) the use of gene therapy methods to transfer a gene into target neurons with (2) the use of optics and electronics (optronics) to deliver the light to the transduced cells. Optogenetics holds clinical promise in the field of vision impairment or degenerative neurological disorders.

About Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a family of orphan genetic diseases caused by multiple mutations in numerous genes involved in the visual cycle. Over 100 genetic defects have been implicated. RP patients generally begin experiencing vision loss in their young adult years, with progression to blindness by age 40. RP is the most widespread hereditary cause of blindness in developed nations, with a prevalence of about 1.5 million people throughout the world. In Europe and the United States, about 350,000 to 400,000 patients suffer from RP, and every year between 15,000 and 20,000 new patients with RP lose sight. There is currently no curative treatment for RP.

About the PIONEER Phase I/II trial

PIONEER is a first-in-man, multi-center, open label dose-escalation study to evaluate the safety and tolerability of GS030 in 12-18 subjects with late-stage retinitis pigmentosa. GS030 combines a gene therapy (GS030-DP) administered via a single intravitreal injection with a wearable optronic visual stimulation device (GS030-MD). Eligible patients in the first three cohorts are those affected by end-stage non-syndromic RP with no light perception (NLP) or light perception (LP) levels of visual acuity. The extension cohort will include patients with hand motion (HM) and counting fingers (CF) levels of visual acuity.

As per protocol, three cohorts with three subjects each will be administered an increasing dose of GS030-DP via a single intravitreal injection in their worse-seeing eye. An extension cohort will receive the highest tolerated dose. The DSMB will review the safety data of all treated subjects in each cohort and will make recommendations before a new cohort receives the next dose. The primary outcome analyses will be on the safety and tolerability at one year post-injection. PIONEER is being conducted in three centers in the United Kingdom, France and the United States.