Press Release

GenSight Biologics Announces the Publication in *Communications Biology* of the Proof-of-Concept for GS030-Drug Product in Non-Human Primates

- First publication to document high spatiotemporal resolution and pattern discrimination by retinal ganglion cells expressing ChrimsonR-tdT in non-human primates
- Findings are compatible with vision restoration at a visual acuity above the legal threshold for blindness defined by the World Health Organization

Paris, France, February 4, 2021, 7:30 am CET – 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 journal *Communications Biology* has published results from the study of GS030-Drug Product (GS030-DP) in non-human primates (NHP).

The paper*, published in the January issue under the title "**Optogenetic therapy: high spatiotemporal resolution and pattern discrimination compatible with vision restoration in non-human primates**", is the first peer-reviewed article constituting a proof-of-concept for retinal ganglion cell (RGC) activation following optogenetic gene therapy with GS030-DP (rAAV2.7m8-ChrimsonR-tdT) in non-human primates. Specifically, the spatiotemporal activation of RGCs allowed for pattern discrimination leading to an estimated Snellen visual acuity of 20/249, superior to the level of legal blindness.

"We are proud to have these results, which have been used to support the IND approval of our Phase I/II clinical trial PIONEER with GS030, published in *Communications Biology,"* commented **Bernard Gilly**, Co-founder and Chief Executive Officer of GenSight. *"This Phase I/II clinical trial is currently recruiting retinitis pigmentosa patients with bare light perception and its objective is to demonstrate that NHP observations translate into useful visual restoration in these patients".*

GS030-DP (rAAV2.7m8-ChrimsonR-tdT) is an optimized viral vector expressing the light-sensitive opsin ChrimsonR. When activated by amber light, ChrimsonR renders its host cell photosensitive, a function lost in retinal diseases causing the degeneration of photoreceptors. Optogenetics combine the cellular expression of light-sensitive opsins with fine-tuned light stimulation generated by a wearable optronic visual stimulation device (GS030-MD).

Preclinical studies generated key findings that supported the initiation of the first-in-human Phase I/II clinical trial PIONEER evaluating the safety and tolerability of the GS030 combined therapy (GS030-DP + GS030-MD) in patients with late-stage retinitis pigmentosa.

"*This preclinical study represents an important milestone towards the clinical validation of this approach to restore some vision in blinding retinal conditions. This journey that started more than a decade ago with*

the collaboration between my team at Institut de la Vision in Paris[a] and Pr. Botond Roska, has also benefited from scientific synergies with the team of Ed Boyden at the MIT," said **José-Alain Sahel, MD,** co-founder of GenSight and of the Institut de la Vision, Director of the IHU FOReSIGHT and Chairman of the Department of Ophthalmology at University of Pittsburgh School of Medicine. "*We expect that the results of the clinical trial PIONEER will indeed confirm the potency of the approach in the interest of patients.*"

Expression of ChrimsonR-tdT in the retina of non-human primates was safe and well tolerated

The intravitreal injection of rAAV2.7m8-ChrimsonR-tdT and the expression of ChrimsonR-tdT in the retina did not induce any significant immune reaction or intraocular inflammation. Under ambient lighting, no photophobia or vision-related changes in behavior was noted in any of the animals injected with rAAV2.7m8-ChrimsonR-tdT. Of note, the wavelength of amber light needed to activate ChrimsonR is much safer than that of highly phototoxic blue-shifted lights.[2]

The AAV2.7m8 vector showed high transduction efficiency in retinal ganglion cells (RGCs)

The modified viral vector AAV2.7m8 was generated using *in vivo*–directed evolution and selected for its ability to efficiently transduce retina cells when injected in the vitreous.[1] The article authored by Gauvain *et al*. showed that, in macaques injected intravitreally, AAV2.7m8 transduced RGCs more efficiently than the wild-type AAV2 vector. A strong cellular expression of ChrimsonR-tdT was observed in the perifovea, where RGCs are most concentrated. Interestingly, the fluorescent marker protein td-Tomato fused to ChrimsonR seemed to increase the expression of functional opsin.

The therapeutic dose of rAAV2.7m8-ChrimsonR-tdT was defined as 5×10^{11} vg/eye, which allowed for greater light sensitivity and higher cellular expression in a wider area of the retina.

ChrimsonR-tdT generated a photocurrent with high temporal and spatial resolution

In functional assays (256-mutlielectrode arrays), the RGCs expressing ChrimsonR-tdT were only activated by amber light at a minimal intensity of 10^{15} photons cm^{-2} s^{-1} and did not show any response to ambient light.

The *ex vivo* retinal stimulation assays also showed that the electrophysiologic response of RGCs expressing ChrimsonR precisely followed the duration and frequency of the light pulses used to activate the opsin. Moreover, localized stimulation of RGCs induced a response coherent with the size and position of the light pulses.

Optogenetic stimulation of RGCs expressing ChrimsonR-tdT can support restoration of visual acuity

The electrophysiological activity of RGCs expressing ChrimsonR-tdT was consistent with the direction and speed of a moving stimulus. Furthermore, the spatiotemporal activation of treated retinas was specific to the shape of the moving symbols presented (square, circle, cross of different sizes), indicating the ability to discriminate between patterns. This level of pattern discrimination corresponded to a Snellen visual acuity of 20/249 (1.1 LogMAR), a level above the threshold of blindness (20/400) defined by the World Health Organization.[3] The authors concluded that "These results lay the groundwork for the ongoing clinical trial, PIONEER, with the AAV2.7m8-ChrimsonR-tdT vector for vision restoration in patients with retinitis pigmentosa."

The paper is available at https://www.nature.com/articles/s42003-020-01594-w.

[a] Serge Picaud, Jens Duebel, Deniz Dalkara and Gregory Gauvain

GenSight Biologics expect to release early findings in the first patients of the PIONEER trial later in the first half of 2021.

***About the paper:**

Optogenetic therapy: high spatiotemporal resolution and pattern discrimination compatible with vision restoration in non-human primates

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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's 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. In diseases causing degeneration of photoreceptors, a therapeutic gene encoding a light-sensitive protein (ChrimsonR-tdT) is introduced into retinal ganglion cells (RGC) to turn them into photosensitive cells, and thereby restore the ability of the retina to respond to light. Chrimson-tdT is a light-sensitive channelrhodopsin that is activated by high intensities of amber light. An external wearable medical device is therefore needed to stimulate the treated retina. The light-stimulating goggles (GS030-MD) encode the visual scene in real-time and project a light beam at a specific wavelength and intensity onto the treated retina. Treatment with GS030 requires that patients wear the external wearable device to enable restoration of 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 developing GS030 combined optogenetic therapy to restore vision in patients suffering from retinitis pigmentosa (RP). Of note, GenSight's optogenetics approach is independent from the specific genetic mutations causing blindness. This technology could be applied to other diseases of the retina in which photoreceptors degenerate, like dry age-related macular degeneration (dry-AMD).

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 result, it is a neuromodulation method that 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 the use of gene therapy methods to transfer a gene into target neurons with the use of optics and electronics (optronics) to deliver the light to the transduced cells. Optogenetics is widely used by research laboratories throughout the world and holds clinical promise in the field of vision impairment or degenerative neurological disorders.

About Retinitis Pigmentosa (RP)

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 existing curative treatment for RP.