Press Release

GenSight Biologics Announces Publication of 5-Year Outcomes for Patients Treated Unilaterally with LUMEVOQ® Gene Therapy

- Five years after the one-time injection, patients with Leber Hereditary Optic Neuropathy (LHON) due to the *MT-ND4* gene variant demonstrated sustained bilateral improvement in visual acuity and favorable safety profile.
- The RESTORE study provides the first long-term benefit-risk assessment of gene therapy in LHON from a Phase III study.

Paris, France, Wednesday, January 15, 2025, 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 the publication of outcomes data from five years' follow-up of patients treated unilaterally with LUMEVOQ®, the company's investigational gene therapy for Leber Hereditary Optic Neuropathy (LHON) due to a mutated *ND4* mitochondrial gene. The patients had all participated in the Phase III trials RESCUE and REVERSE and accepted enrolling into the long-term study RESTORE at the end of the RESCUE and REVERSE studies.

The paper, published online by the leading journal *JAMA Ophthalmology* in December 2024, found that patients "demonstrated a sustained bilateral improvement in BCVA [Best-Corrected Visual Acuity] and a good safety profile over 5 years after treatment". The "persistent benefit" continues the durable effect observed at earlier time points and represents a significant addition to the body of evidence on the benefit-risk ratio of LUMEVOQ® gene therapy in *ND4* LHON patients.

"*The findings on the persistence of visual improvement show the promise of using LUMEVOQ gene therapy to treat patients with LHON due to the MT-ND4 gene variant*," noted **Prof. Patrick Yu-Wai-Man**, **MD, PhD,** Professor of Ophthalmology and Honorary Consultant Neuro-ophthalmologist at the University of Cambridge, Moorfields Eye Hospital, and the UCL Institute of Ophthalmology, United Kingdom, lead author and Principal Investigator in the RESCUE, REVERSE and RESTORE studies. "*The results are especially encouraging given the poor visual prognosis of MT-ND4 LHON, which is the most frequent and severe clinical form of this rare mitochondrial genetic disease*."

When RESTORE participants enrolled in the study, 2 years after the one-time injection, they had already experienced clinically meaningful improvement relative to the lowest point (the "nadir") of their Best-Corrected Visual Acuity (BCVA): +20 ETDRS letters equivalent in their LUMEVOQ®-treated eyes and +17 ETDRS letters equivalent in their sham-treated eyes. Five years after treatment, the bilateral improvement from nadir was sustained, with LUMEVOQ®-treated eyes achieving a mean improvement against nadir of +22 letters equivalent and sham-treated eyes demonstrating a mean improvement of +20 letters equivalent.

Table 1. Change in BCVA Vs. Nadir* In LUMEVOQ® Long-Term Follow-Up (RESTORE)

	2 Years Post-Injection		*5 Years Post-Injection*	
	LogMAR *Mean (SD)*	**Letters Equivalent****	**LogMAR** *Mean (SD)*	**Letters Equivalent****
LUMEVOQ®-treated eyes	-0.4 *(0.4)*	**+20**	-0.4 *(0.5)*	**+22**
Sham-treated eyes	-0.3 *(0.3)*	**+17**	-0.4 *(0.4)*	**+20**

SD: Standard Deviation. Imputed data in alignment with the statistical analysis plan. Figures in this table were extracted from eTable 2 of the article. The RESTORE sample consists of the RESCUE and REVERSE participants who accepted to be followed in the long-term follow-up study. *Nadir = worst best-corrected visual acuity recorded from baseline to time point of interest. **Assessments of best-corrected visual acuity (BCVA) were recorded in LogMAR. The change from nadir in LogMAR was converted to "**letters equivalent**" improvement by multiplying the LogMAR by -50 (ref. J.T. Holladay, *J Refrac Surgery*, 1997;13, 388-391).

Responder analyses at Year 5 indicate that improved BCVA was a benefit for a substantial proportion of the study participants. 66.1% of RESTORE participants achieved clinically meaningful (at least +3 lines' improvement) from nadir in at least one eye, and the proportion rises to 71.0% if the criterion used is Clinically Relevant Recovery (CRR)[1] against nadir. At the end of the five-year follow-up period, 80.6% of participants had on-chart vision (BCVA ≤ 1.6 LogMAR) in at least one eye.

The impact of such results on patients is demonstrated by increases in the self-reported quality of life (QoL) scores at Year 5 vs. baseline. Clinically significant improvement from baseline was observed in 7 of 10 subscale scores of the NEI VFQ-25 questionnaire used to assess quality of life. The composite score showed a clinically meaningful gain of 7 points from baseline.

Safety findings at 5 years post-injection were consistent with previous readouts, which concluded that LUMEVOQ® is well-tolerated. The systemic safety was excellent and most ocular events were mild, none were severe or serious, and none led to study discontinuation.

RESTORE is one of the largest long-term follow-up studies for a rare disease treatment, with 62 participants accepting the invitation to enroll. All participants were treated with a single intravitreal injection of LUMEVOQ® in one eye and with sham injection in the other.

The full article is available online on **this link**.

Definition:

1. Clinically Relevant Recovery (CRR) corresponds to an improvement of at least 0.2 LogMAR (for on-chart eyes) or a movement from off-chart to on-chart (for off-chart eyes).

Contacts

GenSight Biologics
Chief Financial Officer
Jan Eryk Umiastowski
jeumiastowski@gensight-biologics.com

LifeSci Advisors
Investor Relations
Guillaume van Renterghem
gvanrenterghem@lifesciadvisors.com
+41 (0)76 735 01 31

About GenSight Biologics

GenSight Biologics S.A. is a clinical-stage biopharma company focused on discovering and developing 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, GS010, is in Phase III trials in Leber Hereditary Optic Neuropathy (LHON), a rare mitochondrial disease that leads to irreversible blindness in teens and young adults. 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 Leber Hereditary Optic Neuropathy (LHON)

Leber Hereditary Optic Neuropathy (LHON) is a rare maternally inherited mitochondrial genetic disease, characterized by the degeneration of retinal ganglion cells that results in brutal and irreversible vision loss that can lead to legal blindness, and mainly affects adolescents and young adults. LHON is associated with painless, sudden loss of central vision in the 1st eye, with the 2nd eye sequentially impaired. It is a symmetric disease with poor functional visual recovery. 97% of patients have bilateral involvement at less than one year of onset of vision loss, and in 25% of cases, vision loss occurs in both eyes simultaneously.

About LUMEVOQ® (GS010; lenadogene nolparvovec)

LUMEVOQ® (GS010; lenadogene nolparvovec) targets Leber Hereditary Optic Neuropathy (LHON) by leveraging a mitochondrial targeting sequence (MTS) proprietary technology platform, arising from research conducted at the Institut de la Vision in Paris, which, when associated with the gene of interest, allows the platform to specifically address defects inside the mitochondria using an AAV vector (Adeno-Associated Virus). The gene of interest is transferred into the cell to be expressed and produces the functional protein, which will then be shuttled to the mitochondria through specific nucleotidic sequences in order to restore the missing or deficient mitochondrial function. "LUMEVOQ" was accepted as the invented name for GS010 (lenadogene nolparvovec) by the European Medicines Agency (EMA) in October 2018. LUMEVOQ® (GS010; lenadogene nolparvovec) has not been registered in any country at this stage.

About RESCUE, REVERSE, and RESTORE

RESCUE and REVERSE were two separate randomized, double-masked, sham-controlled Phase III trials designed to evaluate the efficacy of a single intravitreal injection of GS010 (rAAV2/2-*ND4*) in participants affected by LHON due to the G11778A mutation in the mitochondrial *ND4* gene.

The primary endpoint measured the difference in efficacy of GS010 in treated eyes compared to sham-treated eyes based on Best-Corrected Visual Acuity (BCVA), as measured with the ETDRS at 48 weeks post-injection. The patients' LogMAR (Logarithm of the Minimal Angle of Resolution) scores, which are derived from the number of letters patients read on the ETDRS chart, were used for statistical purposes. Both trials were adequately powered to evaluate a clinically relevant difference of at least 15 ETDRS letters between drug-treated and sham-treated eyes, adjusted to baseline.

The secondary endpoints involved the application of the primary analysis to best-seeing eyes that received GS010 compared to those receiving sham, and to worse-seeing eyes that received GS010 compared to those that received sham. Additionally, a categorical evaluation with a responder analysis was performed, including the proportion of patients who maintained vision (< ETDRS 15L loss), the proportion of patients who gained 15 ETDRS letters from baseline and the proportion of patients with Snellen acuity of >20/200. Complementary vision metrics included automated visual fields, optical coherence tomography, and color and contrast sensitivity, in addition to quality-of-life scales, bio-dissemination and the time course of immune response. Readouts for these endpoints were at 48, 72 and 96 weeks after injection.

The trials were conducted in parallel, in 37 participants for REVERSE and 39 participants for RESCUE, in 7 centers across the United States, the UK, France, Germany and Italy. Week 96 results were reported in 2019 for both trials, after which patients were invited to participate in a long-term follow-up study, RESTORE, for three additional years.

The primary objective of RESTORE was to assess the long-term safety of intravitreal LUMEVOQ® administration up to 5 years post-treatment. The secondary objective was to assess the long-term treatment efficacy of the therapy and the quality of life (QoL) in participants up to 5 years post-treatment. The first subject was enrolled on January 9, 2018. 61 participants enrolled.

ClinicalTrials.gov Identifiers:
REVERSE: NCT02652780; RESCUE: NCT02652767; RESTORE: NCT03406104