Press Release

GenSight Biologics Announces Publication of Results from LUMEVOQ® RESCUE Pivotal Phase III Trial in AAO journal *Ophthalmology*®

- Bilateral improvement in visual acuity from a unilateral injection of gene therapy – consistent with REVERSE trial findings
- Significant improvement against visual acuity nadir

Paris, France, January 13, 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 of the American Academy of Ophthalmology, *Ophthalmology*®, has published results from the RESCUE pivotal Phase III clinical trial of LUMEVOQ® gene therapy in *ND4* Leber Hereditary Optic Neuropathy (LHON) subjects. The paper*, published in the January issue under the title, "Efficacy and safety of intravitreal gene therapy for Leber hereditary optic neuropathy treated within 6 months of disease onset", is the second peer-reviewed article based on Phase III clinical trial data to document comparable bilateral improvement in visual outcomes from a unilateral injection of a gene therapy.

"*The improvement from nadir in both eyes is compelling and not consistent with what we know about the natural history of this disease*," said **Dr. Nancy J. Newman, MD,** lead author, RESCUE principal investigator and *LeoDelle Jolley* Professor of Ophthalmology and Neurology at the Emory University School of Medicine in Atlanta, GA, USA.

"*The study confirms the clinical benefit of rescuing retinal ganglion cells and optic nerve fibers with Mitochondrial Targeting Sequence (MTS)-based gene therapy*," said **Dr. José-Alain Sahel, MD**, co-founder of GenSight and Director of the *Institut de la Vision* (Sorbonne-Université/Inserm/CNRS), Paris, France, where LUMEVOQ®'s underlying mitochondrial targeting technology was developed. "*Numerous other mitochondrial diseases could be efficiently targeted as demonstrated in this pivotal clinical trial*," added Dr. Sahel, who is also Chairman of the Department of Ophthalmology at *Centre Hospitalier National d'Ophtalmologie des XV-XX*, Paris, France, and Professor and Chairman of the Department of Ophthalmology at the University of Pittsburgh School of Medicine and UPMC (University of Pittsburgh Medical Center), USA.

RESCUE trial data and analyses were key components of the data package submitted by GenSight Biologics in September 2020 to the European Medicines Agency when it applied for marketing authorization for LUMEVOQ® as treatment for patients with visual loss due to LHON caused by a confirmed mutation in the *ND4* mitochondrial gene. The agency's decision is expected in Q4 2021.

Meanwhile, topline results for a third Phase III trial, REFLECT, are expected in Q2 2021.

Key RESCUE Trial outcomes

39 *ND4* LHON subjects, who experienced vision loss within 6 months in at least one eye and vision loss of no longer than 6 months in both eyes at time of enrollment, participated in the RESCUE trial. As in the REVERSE trial, one eye received LUMEVOQ® gene therapy through an intravitreal injection while the other eye received a sham injection. The subjects were followed for 96 weeks after their injection; topline results at Week 96 were reported in 2019.

Efficacy analysis from 38 subjects[1] show that best-corrected visual acuity (BCVA) evolved along parallel trajectories for LUMEVOQ®-treated and sham-treated eyes, deteriorating to the worst levels at Week 24, followed by a plateau phase until Week 48, then showing improvement up to Week 96. By Week 96, average change against the worst recorded BCVA, or nadir, was -0.53 LogMAR (+26 ETDRS letters equivalent) in LUMEVOQ®-treated eyes and -0.46 LogMAR (+23 ETDRS letters equivalent) in sham-treated eyes. This improvement was statistically significant in both eye groups ($p<0.0001$).

At Week 96, 71% of subjects had an improvement of at least -0.3 LogMAR (+15 ETDRS letters equivalent) from the nadir in at least one eye and 71% of subjects had Clinically Relevant Recovery (CRR) from nadir in at least one eye. CRR, a measure of treatment response established by an international consensus meeting on the management of LHON[2], is defined as either an improvement from off-chart BCVA to on-chart, or an on-chart improvement BCVA of at least -0.2 LogMAR, or +10 ETDRS letters.

Improvement in quality of life metrics relative to baseline values taken before treatment, as assessed by the well-established National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), was clinically relevant[3] in the subscales related to mental health, dependency, and role difficulties.

Other topics discussed

The paper also presents detailed safety data, which document that LUMEVOQ® was well-tolerated, with no occurrences of study discontinuation related to ocular adverse events. Ocular adverse events were graded mild or moderate and were resolved without sequelae using standard therapy. Additionally, the authors discuss the coherence of the results with those from the REVERSE trial[4], whose subjects represented patients in later stages of the disease. They note that the observed improvement in visual outcomes in both trials is not aligned with the reported natural history of visual outcomes in LHON patients.

The paper can be obtained on https://www.sciencedirect.com/science/article/pii/S0161642020311878.

***About the paper:**

Efficacy and safety of intravitreal gene therapy for Leber hereditary optic neuropathy treated within 6 months of disease onset

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Notes:

[1] One subject who received a lower dose than planned in the protocol was excluded from the efficacy analyses.

[2] Carelli V, Carbonelli M, De Coo IF, et al. International consensus statement on the clinical and therapeutic management of leber hereditary optic neuropathy. *J Neuro-Ophthalmology*. 2017;37:371-381.

[3] Suñer IJ, Kokame GT, Yu E, et al. Responsiveness of NEI VFQ-25 to changes in visual acuity in neovascular AMD: validation studies from two phase 3 clinical trials. *Invest Ophthalmol Vis Sci*. 2009;50:3629-3635.

[4] Yu-Wai-Man P, Newman NJ, Carelli V, et al. Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy. *Sci. Transl. Med.* 2020; 12: eaaz7423. 9 December 2020.

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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 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. The estimated incidence of LHON is approximately 800-1,200 new patients who lose their sight every year in the United States and the European Union.

About LUMEVOQ® (GS010)

LUMEVOQ® (GS010) 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.

About RESCUE and REVERSE

RESCUE and REVERSE are 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 subjects 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, was used for statistical purposes. Both trials were adequately powered to evaluate a clinically relevant difference of at least 15 ETDRS letters between treated and untreated 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 evaluated, including the proportion of patients who maintain vision (< ETDRS 15L loss), the proportion of patients who gain 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 subjects for REVERSE and 39 subjects 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 a long-term follow-up study that will last for three years.

ClinicalTrials.gov Identifiers:
REVERSE: NCT02652780
RESCUE: NCT02652767