Press Release

GenSight Biologics Announces Publication of Results from LUMEVOQ® REVERSE Pivotal Phase III Trial and Non-Human Primate Study in *Science Translational Medicine*

- First publication based on Phase III data to document sustained and clinically meaningful bilateral improvement in visual acuity from unilateral injection of a gene therapy
- Non-human primate study clarifies mechanism behind contralateral effect

Paris, France, December 10, 2020, 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 *Science Translational Medicine* has published results from the REVERSE pivotal Phase III clinical trial of LUMEVOQ® gene therapy in *ND4* Leber Hereditary Optic Neuropathy (LHON) subjects along with key results from a non-human primate study investigating the contralateral effect of the gene therapy. The paper*, published in the December issue under the title "Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy", is the first peer-reviewed article based on Phase III clinical trial data to document sustained and clinically meaningful bilateral improvement in visual outcomes from a unilateral injection of a gene therapy.

The findings from the REVERSE trial and the non-human primate study 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.

"The treatment has been shown to be safe and the outcomes can be life changing," said **Dr. Patrick Yu-Wai-Man, MD, PhD**, lead author, REVERSE principal investigator and Senior Lecturer and Honorary Consultant Ophthalmologist at the University of Cambridge, Moorfields Eye Hospital, and the UCL Institute of Ophthalmology, London, United Kingdom.

"Our study provides great hope for treating this blinding disease in young adults," said **Dr. José-Alain Sahel, MD**, co-corresponding author, 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. "Our approach isn't just limited to vision restoration: other mitochondrial diseases could be treated using the same technology," 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.

REVERSE Trial outcomes

37 *ND4* LHON subjects, who experienced onset of vision loss from 6 months to one year before enrollment, participated in the REVERSE trial. The results show a clinically meaningful improvement over baseline of +15 ETDRS letters (−0.308 LogMAR) in the average best-corrected visual acuity (BCVA) of injected eyes of the 37 REVERSE patients 96 weeks after treatment. The patients' other eye, which received a sham injection, experienced an average visual acuity gain over baseline of +13 letters equivalent (−0.259 LogMAR). Against nadir, or the worst recorded BCVA, the gains were even more impressive, at +28.5 ETDRS letters for the LUMEVOQ®-injected eyes and +24.5 ETDRS letters for sham-injected eyes.

81% of subjects showed a clinically relevant recovery (CRR) from the nadir in one or both eyes. CRR, a measure of treatment response established by an international consensus meeting on the management of LHON[1], 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.

The improvement in quality of life metrics relative to baseline values taken before treatment, which were evaluated using the well-established National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), was compelling and largely above the thresholds of clinical relevance. The composite NEI VFQ-25 score showed a mean improvement of 9.5 points, exceeding the clinically relevant threshold of +3.9-+4.3 points.[2]

Non-human primate study outcomes

The non-human primate study, launched to investigate the mechanism behind the unexpected improvement in the contralateral eye's visual function, was designed to mimic the REVERSE trial, with monkeys given a unilateral LUMEVOQ® injection. The study demonstrated the transfer of viral vector DNA from the injected eye to the anterior segment, retina, and optic nerve of the noninjected eye. This result, the authors conclude, provides a plausible mechanistic explanation for the bilateral improvement in visual function after unilateral LUMEVOQ® injection.

Other topics discussed

The paper also presents detailed safety data, which document the overall good safety profile of LUMEVOQ®, with no viral vector biodissemination and mostly mild ocular adverse events that were controlled with local topical therapy. Additionally, the authors discuss other results from REVERSE, such as other responder analyses and visual outcomes, and place these in context against the natural history insights found in analyses of visual acuity in non-treated patients.

The paper can be obtained from www.sciencemag.org.

***About the paper:**

Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy

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Notes:

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[2] I. J. Suñer, G. T. Kokame, E. Yu, J. Ward, C. Dolan, N. M. Bressler, 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.* **50**, 3629–3635 (2009).

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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