Press Release

GenSight Biologics Announces Publication of Non-Human Primate Study Reporting Presence of LUMEVOQ® Vector DNA in Contralateral Eyes After Unilateral Injection

- Study demonstrates contralateral transfer of LUMEVOQ® after unilateral injection
- Results suggest mechanistic explanation for bilateral improvement of visual function among *ND4*-LHON patients unilaterally treated with LUMEVOQ®

Paris, France, December 1, 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 *Molecular Therapy – Methods and Clinical Development* has published the results of a mechanistic study demonstrating the transfer of LUMEVOQ® vector DNA from the injected eyes to the non-injected eyes of non-human primates.

The findings provide a mechanistic explanation for the bilateral improvement of best-corrected visual acuity (BCVA) observed in *ND4*-LHON patients unilaterally treated with a single intravitreal (IVT) injection of LUMEVOQ®, which was observed in all clinical trials of the gene therapy (unilaterally treated patients in REVEAL; RESCUE, REVERSE and RESTORE studies; and the unilaterally treated patients in the REFLECT study).[a,b,c,d]

"*This work is consistent with our previous report published last year in Science Translational Medicine and by illuminating the unexpected bilateral effect, addresses some of the questions that arose when the contralateral effect was so consistently observed across the LUMEVOQ trials,"* commented last and corresponding author **José-Alain Sahel, MD**, Co-founder of GenSight Biologics and of the *Institut de la Vision* (Sorbonne-Université/Inserm/CNRS), Paris, France, and Distinguished Professor and Chairman of the Department of Ophthalmology at the University of Pittsburgh School of Medicine, USA. "*The implications for the design of future gene therapy trials are significant."*

Lead author **David J. Calkins, PhD**, O'Day Professor & Vice Chair and Director for Research at the Department of Ophthalmology and Visual Sciences at Vanderbilt University Medical Center, further noted, "*Our study is a critical step towards understanding not only how bilateral improvement in vision occurs with unilateral gene therapy, but also mechanisms of interocular interactions more generally. Crosstalk between the two optic projections could have ramifications for additional blinding eye diseases*."

In the LUMEVOQ® clinical studies, BCVA improved in both eyes of patients who received a unilateral injection of the gene therapy. The mechanism behind the contralateral therapeutic effect of LUMEVOQ® on untreated eyes was explored in a non-human primate (NHP) study that analyzed the biodistribution of LUMEVOQ® vector DNA (*i.e.,* the therapeutic *ND4* gene) in the visual system following a single unilateral IVT. Six monkeys received a single injection of LUMEVOQ® in their right eye at a dose equivalent to that used in humans. Three of these monkeys were monitored for 3 months and the other three for 6 months. Two control animals were monitored for 3 and 6 months but received a placebo injection.

As expected, LUMEVOQ® vector DNA was detected in all the eyes that were injected with the gene therapy. But vector DNA was also detected or quantified in the contralateral non-injected eyes for 5 of the 6 animals in the treatment group. In addition, vector DNA was detected or quantified in the optic chiasm of all 6 animals. The results provide evidence that LUMEVOQ® vector DNA reached the non-injected eye after unilateral IVT.

Because biodissemination studies have detected only a limited and transient presence of vector DNA in the blood of *ND4*-LHON patients treated with LUMEVOQ®, systemic transfer of vector DNA was ruled unlikely as the mechanism behind the results. The investigators instead consider transport via the optic nerve and chiasm along the anterior visual pathways as the likely mechanism for the transfer of the viral vector DNA to the untreated eye.

The authors also discuss other mechanisms that could participate in the contralateral treatment effect of LUMEVOQ®, such as the transfer of mitochondrial material (like RNA or proteins) between eyes and brain plasticity.

The paper is available at https://www.sciencedirect.com/science/article/pii/S2329050121001510. The article will be in the December 10 print issue of the journal.

***About the paper:**

Biodistribution of Intravitreal Lenadogene Nolparvovec Gene Therapy in Nonhuman 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 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; 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.