Press Release

GenSight Biologics Announces Publication Analyzing Visual Parameters of *ND4*-LHON Subjects before LUMEVOQ® treatment in Phase III Trials

- In the first 6 months post-vision loss (RESCUE patients before treatment), each month after onset was associated with a mean visual acuity loss of +0.24 LogMAR (-12 ETDRS letters equivalent)
- Time from onset was not associated with substantial worsening of visual acuity for patients between 6 and 12 months post-vision loss (REVERSE patients before treatment)
- Cross-sectional analysis reinforces knowledge of LHON natural history progression: an acute phase in the first months is followed by relative stabilization during the dynamic phase

Paris, France, September 9, 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 Neuro-Ophthalmology* has published a paper on a cross-sectional analysis of the baseline (pre-treatment) characteristics of the *ND4*-LHON subjects enrolled in the RESCUE and REVERSE Phase III trials of LUMEVOQ®.

The paper*, published in the September issue under the title "Cross-Sectional Analysis of Baseline Visual Parameters in Subjects Recruited into the RESCUE and REVERSE *ND4*-LHON Gene Therapy Studies", confirms drastic loss of visual function and anatomy in the year after onset of vision loss due to Leber hereditary optic neuropathy (LHON) caused by the G11778A mutation in the *ND4* gene.

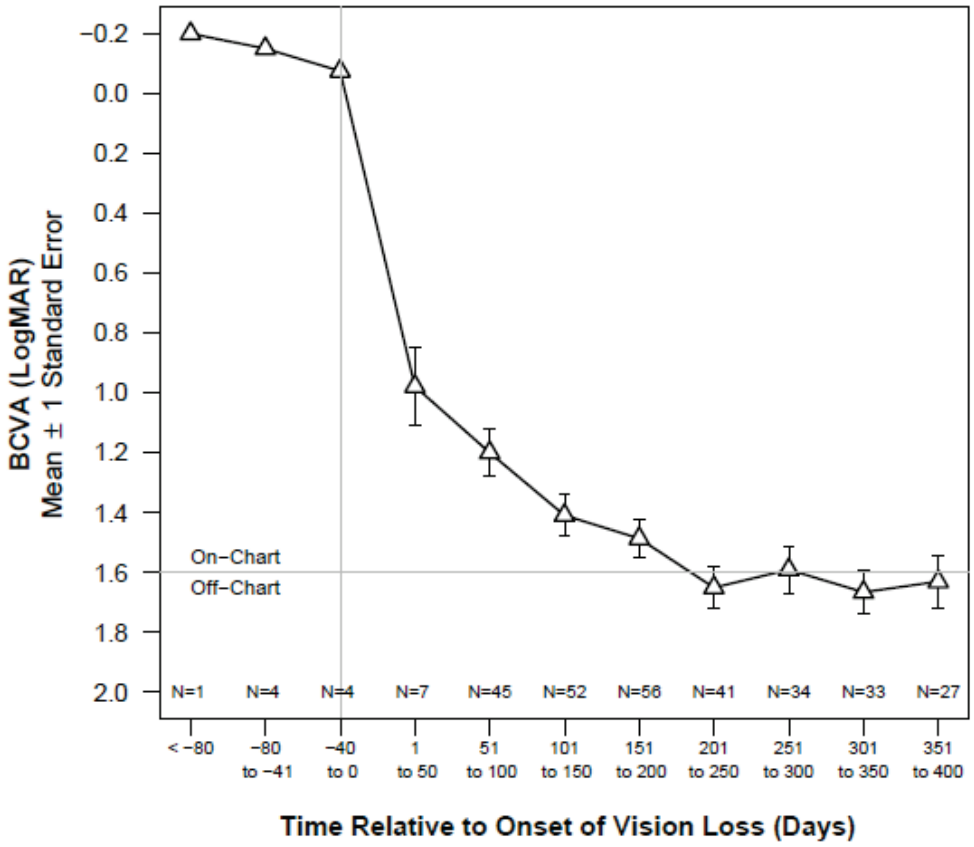
"This cross-sectional analysis of patients with strict examination protocols demonstrates that once symptomatic with ND4-LHON, visual acuity and retinal structures rapidly deteriorate over months to a level of legal blindness," commented lead author **Dr. Mark L. Moster, MD**, Department of Neuro-Ophthalmology, Wills Eye Hospital and Professor of Neurology and Ophthalmology at Thomas Jefferson University, Philadelphia, United-States. Dr. Moster, who was also an Investigator in the RESCUE and REVERSE trials, added, "*These findings emphasize the need for early diagnosis and potential gene therapy in these patients."*

GenSight Biologics' gene therapy LUMEVOQ® was submitted for marketing approval in Europe in September 2020 after RESCUE and REVERSE demonstrated visual acuity improvements among patients treated with LUMEVOQ®.

The cross-sectional analysis of baseline data showed that best-corrected visual acuity (BCVA) values substantially worsened in the first 8 months after onset of vision loss and were globally off-chart after 8 months of vision loss. Linear regression analysis of individual data points showed that each month of vision loss was associated with a mean visual acuity loss of +0.24 LogMAR (-12 ETDRS letters equivalent) in the eyes of untreated RESCUE patients with less than 6 months of vision loss. In the eyes of untreated

REVERSE patients with 6 to 12 months of vision loss, each month was associated with little further visual acuity deterioration (on average +0.02 LogMAR, -1 ETDRS letter equivalent).

Figure 1. BCVA in untreated *ND4*-LHON patients as a function of duration of vision loss



BCVA: best-corrected visual acuity

N: number of observations pooled together to calculate the means. Individual BCVA values were collected at screening and inclusion, then grouped and averaged by time since onset of vision loss. Due to a very low number of observations available before onset of vision loss, no standard error was calculated.

When the RESCUE and REVERSE sub-samples were compared, mean visual acuity, contrast sensitivity, and parameters of retinal anatomy measured by spectral-domain optical coherence tomography (SD-OCT) were significantly worse in eyes with 6 to 12 months of vision loss, compared to those in eyes with up to 6 months of vision loss.

The baseline data were collected on two pre-injection visits among the 76 subjects in the RESCUE and REVERSE clinical trials. At enrollment, subjects were over 15 years old and had between 0 and 6 months of vision loss in RESCUE, and 6 to12 months of vision loss in REVERSE. Baseline data were grouped and averaged according to time since onset of vision loss, in order to describe the variation of visual parameters over the first year after disease onset.

The findings reinforce the medical consensus on the natural history of LHON over the first year post-vision loss, in which an acute phase of visual decline in the first months after onset is followed by a relative stabilization of visual acuity in the dynamic phase of the disease.[a] This pattern, in combination with the very low rate of spontaneous partial recovery of visual acuity in patients with the G1178A mutation and later onset (at 15 and over)[b], suggests that *ND4*-LHON patients matching the RESCUE and REVERSE populations have an acute need for therapeutic intervention.

The paper is available at https://journals.lww.com/jneuro-ophthalmology/Fulltext/2021/09000/Cross_Sectional_Analysis_of_Baseline_Visual.4.aspx .

***About the paper:**

Cross-Sectional Analysis of Baseline Visual Parameters in Subjects Recruited into the RESCUE and REVERSE *ND4*-LHON Gene Therapy Studies

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Notes:

[a] Carelli V, Carbonelli M, de Coo IF, *et al*. International Consensus Statement on the Clinical and Therapeutic Management of Leber Hereditary Optic Neuropathy. *J Neuroophthalmol.* 2017 Dec;37(4):371-381.

[b] Newman NJ, Carelli V, Taiel M, Yu-Wai-Man P. Visual Outcomes in Leber Hereditary Optic Neuropathy Patients with the m.11778G>A (*MTND4*) Mitochondrial DNA Mutation. *Journal of Neuro-Ophthalmology*. 2020 Dec;40(4):547-557.

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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.

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