Press Release

GenSight Biologics Announces Publication of Results from LUMEVOQ® Phase I/IIa Clinical Trial REVEAL in *BioDrugs*

- Early demonstration of favorable LUMEVOQ® safety profile in human subjects subsequently confirmed in later trials
- Dose for Phase III trials selected based on best benefit-risk ratio demonstrated across four cohorts
- Favorable safety and tolerability confirmed over 5-year follow-up period

Paris, France, February 15, 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 *BioDrugs* has published results from REVEAL, the Phase I/IIa clinical trial that evaluated the safety of LUMEVOQ® gene therapy in subjects with *ND4* Leber Hereditary Optic Neuropathy (LHON) and determined the dose subsequently used in the Phase III trials RESCUE and REVERSE.

The paper*, published in the February issue of *BioDrugs* under the title "Safety of intravitreal gene therapy for treatment of subjects with Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial *ND4* gene – The REVEAL study", discusses the results that were the first to demonstrate the favorable safety profile of LUMEVOQ® while also providing signals of efficacy that were more fully investigated in the Phase III trials.

"The REVEAL study demonstrated that treatment with lenadogene nolparvovec (rAAV2/2-ND4, or LUMEVOQ®) is well-tolerated over both the short and long term by LHON patients with the ND4 mutation," commented lead investigator **Dr. Catherine Vignal, MD**, Department of Neuro Ophthalmology and Emergencies, Rothschild Foundation Hospital, Paris, France, and *Centre Hospitalier National d'Ophtalmologie des Quinze Vingts*, Paris, France. *"As the gene therapy's first clinical study, it gave encouraging results and paved the way for the efficacy investigations of the Phase III trials RESCUE and REVERSE."*

"*This study confirms the gene therapy's favorable long-term safety and further demonstrates that the trends that were initially observed have been maintained for at least five years*," said **Dr. José-Alain Sahel, MD**, co-founder of GenSight and founder of the *Institut de la Vision* (Sorbonne-Université/Inserm/CNRS), Paris, France, where LUMEVOQ®'s underlying Mitochondrial Targeting Sequence technology was developed. Dr. Sahel is also the Director of *Institut Hospitalo-Universitaire FOReSIGHT*, and Distinguished Professor and Chairman of the Department of Ophthalmology at the University of Pittsburgh School of Medicine and UPMC (University of Pittsburgh Medical Center), USA.

REVEAL trial data and analyses were integral components of the evidence package submitted by GenSight Biologics in September 2020 to the European Medicines Agency when it filed a Marketing Authorisation Application (MAA) 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.

GenSight Biologics expects to report topline results from its third Phase III trial REFLECT in Q2 2021. The trial will evaluate the efficacy and safety of bilateral injections of LUMEVOQ® in subjects with LHON caused by a mutated *ND4* gene. REFLECT was designed under a Special Protocol Assessment agreement with the US Food and Drug Administration (FDA).

REVEAL Trial Design and Key Results

REVEAL was an open-label, single-center, dose escalation study launched in 2014 that evaluated the safety and tolerability of lenadogene nolparvovec in 15 subjects with *ND4* LHON, who were followed for up to 5 years following a single intravitreal injection to their worst affected eye. No limits were placed on the time since onset of vision loss. Subjects were enrolled sequentially in 4 cohorts of 3 subjects each, with each cohort receiving increasing doses of the gene therapy[a]. Dose escalation proceeded only after a safety evaluation by an independent data safety monitoring board (DSMB). A final extension cohort received the dose that the DSMB determined to have the best benefit-risk ratio among those administered to the four previous cohorts.

LUMEVOQ® treatment was well-tolerated over the 5-year follow-up period. No Serious Adverse Events were considered related to treatment; no unexpected adverse events occurred; and no Grade 3 or 4 Common Terminology Criteria for Adverse Events (CTCE) were reported. Anterior chamber inflammation and vitritis were mostly managed with topical steroids. This safety profile has been subsequently affirmed in the Phase III trials RESCUE and REVERSE.[b]

The occurrence of ocular inflammation was used by the DSMB to recommend $9x10^{10}$ viral genomes [vg]/eye as the optimal dose to carry forward into the Phase III investigation. Despite treatment after considerable time since onset (4.6 years on average after vision loss), the six subjects who received this dose achieved a mean visual acuity improvement over baseline of -0.68 LogMAR for treated eyes, and -0.64 LogMAR for untreated eyes, with a mean (±SD) final value of +1.77 (±0.52) LogMAR and +1.78 (±0.34) LogMAR, respectively. While meaningful, this improvement is less impressive than that observed in the Phase III trials RESCUE and REVERSE, as the subjects in the later trials were treated earlier in the course of their disease.

The paper is available on https://rdcu.be/ce7s4.

***About the paper:**

Safety of intravitreal gene therapy for treatment of subjects with Leber Hereditary Optic Neuropathy due to mutations in the mitochondrial *ND4* gene – The REVEAL study

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Notes:

[a] The four dosages investigated were $9x10^9$ vg/eye [Cohort 1], $3x10^{10}$ vg/eye [Cohort 2], $9x10^{10}$ vg/eye [Cohort 3] and $1.8x10^{11}$ vg/eye [Cohort 4].

[b] See Newman NJ, Yu-Wai-Man P, Carelli V, *et al*. Efficacy and Safety of Intravitreal Gene Therapy for Leber Hereditary Optic Neuropathy Treated within 6 Months of Disease Onset. *Ophthalmology* 2021; In Press, 12 Januuary 2021, and 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; 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