Press Release

GenSight Biologics Confirms Sustained Efficacy and Safety of Bilateral LUMEVOQ® Injections at 2-Year Follow-Up of REFLECT Phase III Trial

- Sustained efficacy two years after injection: statistically significant visual acuity improvement from baseline and nadir in LUMEVOQ®-treated eyes
- 73% of bilaterally treated subjects experienced at least +15 ETDRS letters vs. nadir
- Better efficacy for bilaterally treated subjects, coupled with favorable safety profile

Paris, France, December 14, 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 reported topline efficacy and safety results at 2 years post-treatment administration in the REFLECT Phase III clinical trial with LUMEVOQ®. The results show sustained efficacy and safety for bilateral intravitreal injection of the gene therapy, including better efficacy compared to unilateral injection.

The findings reinforce the results observed at 1.5 years post-treatment administration, which were reported in June 2021.

"*The REFLECT trial's demonstration of a sustained, significant and safe improvement in visual acuity for LHON patients treated bilaterally with LUMEVOQ provides additional impetus for our push to gain regulatory approval*," said **Bernard Gilly**, CEO and Co-Founder of GenSight Biologics. "*Patients afflicted with LHON who are losing their sight deserve access to a treatment like LUMEVOQ*."

Designed under a Special Protocol Assessment with the FDA, REFLECT is a randomized, double-masked, placebo-controlled Phase III trial involving 98 subjects with vision loss due to Leber Hereditary Optic Neuropathy (LHON) caused by a mutated *ND4* mitochondrial gene; enrolled *ND4* subjects had vision loss up to one year from onset. The *ND4* mitochondrial mutation is associated with the most severe clinical form of LHON, with poor overall visual outcomes.[1] All subjects received an intravitreal injection (IVT) of LUMEVOQ® in their first affected eye. The second affected eye was randomized to either a second IVT of LUMEVOQ® or a placebo IVT, which was administered on the same day or the following day. 48 subjects were randomized to LUMEVOQ® bilateral treatment, and 50 to LUMEVOQ® unilateral treatment (first-affected eye treated with LUMEVOQ®, second-affected eye treated with placebo).

Significant visual acuity improvement over baseline, with better results for bilaterally injected patients

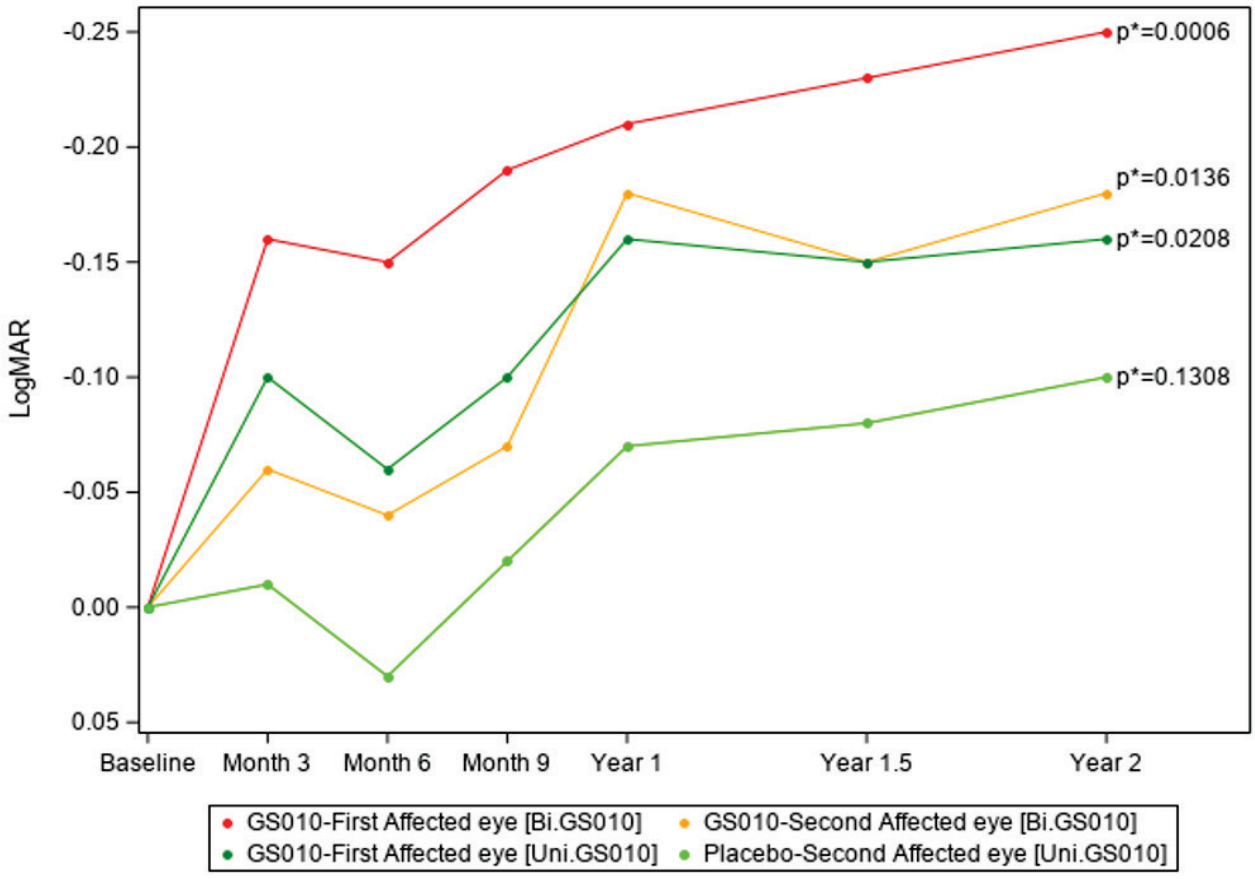
Two years after injection, the mean best-corrected visual acuity (BCVA) in LUMEVOQ®-treated eyes was statistically significantly better than baseline, whereas the improvement from baseline was not statistically significant in placebo-treated eyes. The results indicate a sustained treatment effect for all subjects, with the improvement being greater among bilaterally treated patients.

Table 1: Change in Best-Corrected Visual Acuity (BCVA) versus Baseline, 2 Years after Injection

	1st affected eye	2nd affected eye
Subjects bilaterally injected with LUMEVOQ®	**LUMEVOQ®** **-0.25 LogMAR** **+13 ETDRS letters** ***p=0.0006***	**LUMEVOQ®** **-0.18 LogMAR** **+9 ETDRS letters** ***p=0.01***
Subjects unilaterally injected with LUMEVOQ®	**LUMEVOQ®** **-0.16 LogMAR** **+8 ETDRS letters** ***p=0.02***	**PLACEBO** **-0.10 LogMAR** **+5 ETDRS letters** ***p=0.1 (NS)***

The contralateral effect observed with placebo at 2 years is consistent with that which was documented in *sham*-treated eyes in the REVERSE[2] and RESCUE[3] trials.

Figure 1. Best-Corrected Visual Acuity (BCVA) Change from Baseline (LogMAR) – Eye Groups



Note: Difference from baseline LogMAR. LS means was estimated by mixed models at the eye level, adjusted on baseline, with repeated values for each patient. The p* values are against baseline.

Year 2 analyses also confirm the dose effect that was noted at Year 1.5: the mean BCVA at 2 years for bilaterally and unilaterally treated subjects reached 1.32 and 1.44 LogMAR, respectively, with an absolute difference between arms of +6 ETDRS letters in favor of bilaterally treated subjects.

Responder analyses point to the benefits of treatment for patients that would otherwise have experienced significant vision loss with a very low likelihood of spontaneous recovery.[1] For example, 60% of the bilaterally treated patients (56% of unilaterally treated patients) who had vision above the threshold of legal blindness in at least one eye remained above the threshold at Year 2.

Efficacy demonstrated even more clearly in visual acuity improvement from nadir

Comparison against nadir (i.e., the worst BCVA recorded from baseline to Year 2) more starkly demonstrates the efficacy of LUMEVOQ®, even for the placebo eyes that improved via a contralateral treatment effect.

Table 2: Change in Best-Corrected Visual Acuity (BCVA) versus Nadir, 2 Years after Injection

	1st affected eye	2nd affected eye
Subjects bilaterally injected with LUMEVOQ®	**LUMEVOQ®** **-0.39 LogMAR** **+20 ETDRS letters** ***p<0.0001***	**LUMEVOQ®** **-0.34 LogMAR** **+17 ETDRS letters** ***p<0.0001***
Subjects unilaterally injected with LUMEVOQ®	**LUMEVOQ®** **-0.38 LogMAR** **+19 ETDRS letters** ***p<0.0001***	**PLACEBO** **-0.27 LogMAR** **+14 ETDRS letters** ***p<0.0001***

Responder analyses indicate that the treatment effect is not limited to just a minority of subjects. Two years after injection, 73% of bilaterally treated subjects and 66% of unilaterally treated subjects had experienced a clinically meaningful improvement of at least -0.3 LogMAR (+15 ETDRS letters) relative to their observed nadir.

Table 3: Responder Analyses, Based on Change from Nadir at Year 2

Definition of Responder	-0.3 LogMAR improvement in at least one eye	Clinically Relevant Recovery* in at least one eye
Subjects bilaterally injected with LUMEVOQ®	**73%**	**75%**
Subjects unilaterally injected with LUMEVOQ®	**66%**	**60%**

Note: *"Clinically Relevant Recovery" is defined as: i) For eyes on-chart at nadir, an improvement of ≤ -0.2 LogMAR (≥10 ETDRS letters) from nadir; or ii) For eyes off-chart at nadir, eyes which became on-chart (i.e., BCVA ≤1.6 LogMAR).

Bilateral injections have a favorable safety profile

The favorable safety profile of LUMEVOQ® was confirmed. There was no study discontinuation related to systemic or ocular adverse events, and there were no serious ocular adverse events. The main ocular adverse event was intraocular inflammation, which was mostly mild and responsive to conventional treatment. The favorable safety profile was comparable in unilaterally and bilaterally treated subjects.

"*The persistence of LUMEVOQ efficacy is remarkably consistent across the development program, so that the REFLECT results bolster the evidence provided by 3 years of data from RESTORE[4] and 5 years of data from REVEAL*," noted **Magali Taiel, MD**, Chief Medical Officer of GenSight Biologics.

Results of the 4-year follow-up of RESTORE are expected to be available in January 2022.

Dr. Taiel added, "*Moreover, we affirm the insight that bilateral injection of LUMEVOQ is the best option for patients with ND4 Leber Hereditary Optic Neuropathy*."

REFLECT patients have been invited to participate in a long-term follow-up that will monitor the safety and efficacy of LUMEVOQ® up to 5 years post-injection.

References:

1. Newman NJ, Carelli V, Taiel M, Yu-Wai-Man P. Visual outcomes in Leber hereditary optic neuropathy subjects with the m.11778G>A (MTND4) mitochondrial dna mutation. *J Neuroophthalmol.* (2020) 40:547–57. doi: 10.1097/WNO.0000000000001045.
2. Yu-Wai-Man P, Newman NJ, Carelli V, Moster ML, Biousse V, Sadun AA, et al. Bilateral visual improvement with unilateral gene therapy injection for Leber hereditary optic neuropathy. *Sci Transl Med.* (2020) 12:eaaz7423. doi: 10.1126/scitranslmed.aaz7423
3. Newman NJ, Yu-Wai-Man P, Carelli V, Moster ML, Biousse V, Vignal-Clermont C, et al. Efficacy and safety of intravitreal gene therapy for Leber hereditary optic neuropathy treated within 6 months of disease onset. *Ophthalmology*. (2021) 128:649–60. doi: 10.1016/j.ophtha.2020.12.012.
4. Biousse V, Newman NJ, Yu-Wai-Man P, Carelli V, Moster ML, Vignal-Clermont C, et al. Long-term follow-up after unilateral intravitreal gene therapy for Leber hereditary optic neuropathy: The RESTORE study. *J Neuroophthalmol.* (2021) 41:309-315.

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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 subjects 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 subjects 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 subjects 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 1,200-1,500 new subjects 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 REFLECT

REFLECT is a multi-center, randomized, double-masked, placebo-controlled study to evaluate the safety and efficacy of bilateral injections of GS010 in subjects with LHON due to the NADH dehydrogenase 4 (*ND4*) mutation. In the active arm, GS010 was administered as a single intravitreal injection in each eye of each subject. In the placebo arm, GS010 was administered as a single intravitreal injection to the first affected eye, while the fellow eye received a placebo injection.

The primary endpoint for the REFLECT trial is the BCVA reported in LogMAR at 1.5 years (78 weeks) post-treatment in the second-affected/not-yet-affected eye. The change from baseline in second-affected/not-yet-affected eyes receiving GS010 and placebo is the primary response of interest. The secondary efficacy endpoints include: BCVA reported in LogMAR at 2 years post-treatment in the second-affected/not-yet-affected eye compared to both placebo and the first-affected eye receiving GS010, OCT and contrast sensitivity and quality of life scales.

The trial was conducted in multiple centers across Europe (1 each in France, Spain, Italy and the UK), the US (6 centers) and Taiwan (1 center). The trial planned to enroll 90 subjects with vision loss up to 1 year in duration; 98 subjects were successfully screened and treated. The first subject was treated in March 2018 and the last one in July 2019.

ClinicalTrials.gov Identifiers:
REFLECT: NCT03293524