Press Release

GenSight Biologics Reports Topline Results from REFLECT Phase III Clinical Trial, Confirming LUMEVOQ® Efficacy Including Better Efficacy with Bilateral Treatment

- Statistically significant visual acuity improvement from baseline and nadir in LUMEVOQ®-treated eyes
- Better efficacy for bilaterally treated subjects
- Contralateral effect confirmed, as demonstrated in REVERSE and RESCUE trials
- Favorable safety profile for bilateral treatment
- Key Opinion Leader Call on REFLECT data: July 9 at 8:00 am EDT / 2:00 pm CEST

Paris, France, Wednesday, June 30, 2021, 7.30 am CEST – GenSight Biologics (Euronext: SIGHT, ISIN: FR0013183985, PEA-PME eligible), a biopharma company focused on discovering and developing innovative gene therapies for retinal neurodegenerative diseases and central nervous system disorders, today reported key efficacy and safety findings at 1.5 years (78 weeks) post-treatment in the REFLECT Phase III clinical trial for LUMEVOQ®. The results show better visual acuity improvements from bilateral intravitreal injections of the gene therapy compared to a unilateral injection.

"*Following the rigorous guidelines of pivotal clinical trials, the data from REFLECT confirm that LUMEVOQ gene therapy improved best-corrected visual acuity (BCVA), also the primary outcome for REVERSE and RESCUE*," commented **Dr. Robert Sergott**, Director, Neuro-Ophthalmology Service, Wills Eye Hospital, and Founding Director and CEO, William H. Annesley EyeBrain Center, Thomas Jefferson University, Philadelphia, PA, USA. "*The surprising, ground-breaking, bilateral improvement with unilateral injection was found again, certainly not a chance event in three independent trials.*"

Dr. Sergott added, "*The bilateral injection of LUMEVOQ, showing better efficacy with no tradeoff in terms of safety or tolerability, makes the gene therapy a compelling therapeutic option. LUMEVOQ has changed the lives of patients with Leber Hereditary Optic Neuropathy.*"

Designed under a Special Protocol Assessment with the FDA, the REFLECT trial 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

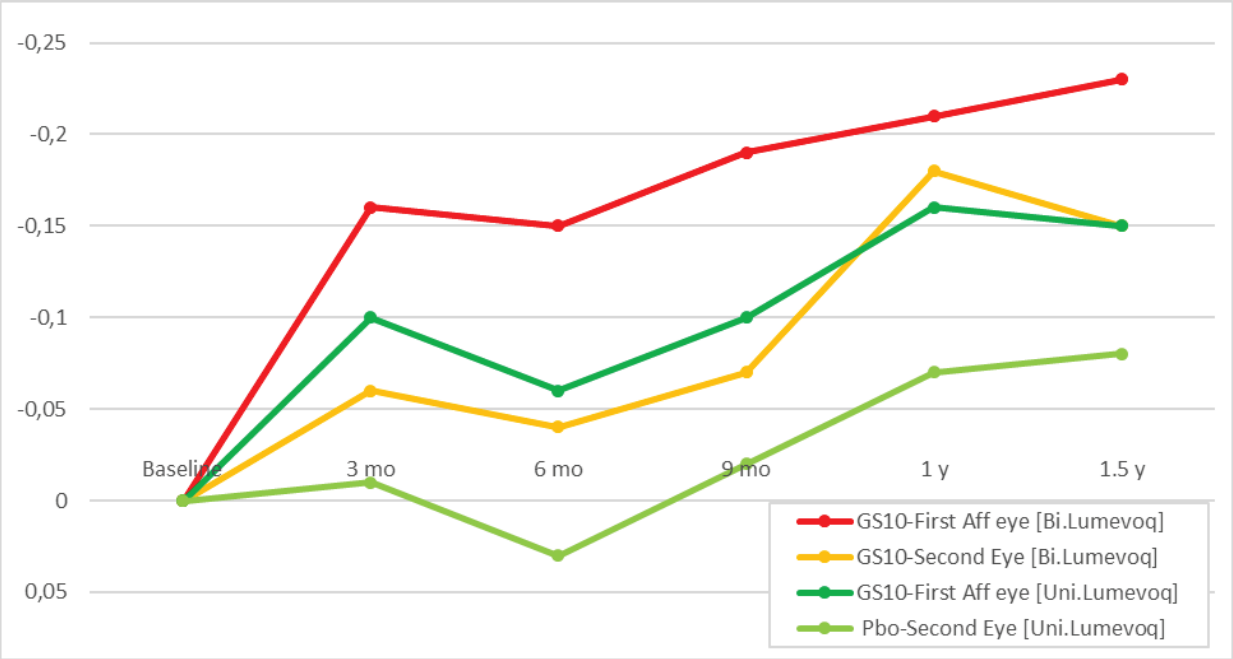
At the primary time point of the analysis, 1.5 years after injection, mean best-corrected visual acuity (BCVA) in LUMEVOQ®-treated eyes was statistically significantly better than baseline, whereas the improvement from baseline was not statistically significant in placebo eyes.

Table 1: Change in Best-Corrected Visual Acuity (BCVA versus Baseline, 1.5 Years after Injection

	1st-affected eye	2nd-affected eye
Bilaterally injected subjects	LUMEVOQ **0.23 LogMAR** (**+12 ETDRS letters** equivalent; *p=0.001***)	LUMEVOQ **0.15 LogMAR** (**+8 ETDRS letters** equivalent; *p<0.05**)
Unilaterally injected subjects	LUMEVOQ **0.15 LogMAR** (**+8 ETDRS letters** equivalent; *p<0.05**)	PLACEBO **0.08 LogMAR** (**+4 ETDRS letters** equivalent; *p=NS*)

Consistent with REVERSE[2] and RESCUE[3], unilaterally treated subjects showed a contralateral effect in their placebo-treated eye (Figure 1). The contralateral effect reduced the difference in the outcomes among LUMEVOQ®- and placebo-treated eyes, and consequently, the trial did not meet the pre-defined primary endpoint. The difference of the change from baseline in BCVA between the second affected LUMEVOQ® and placebo-treated eyes was -0.05 LogMAR (+3 ETDRS letters equivalent; p=0.6080).

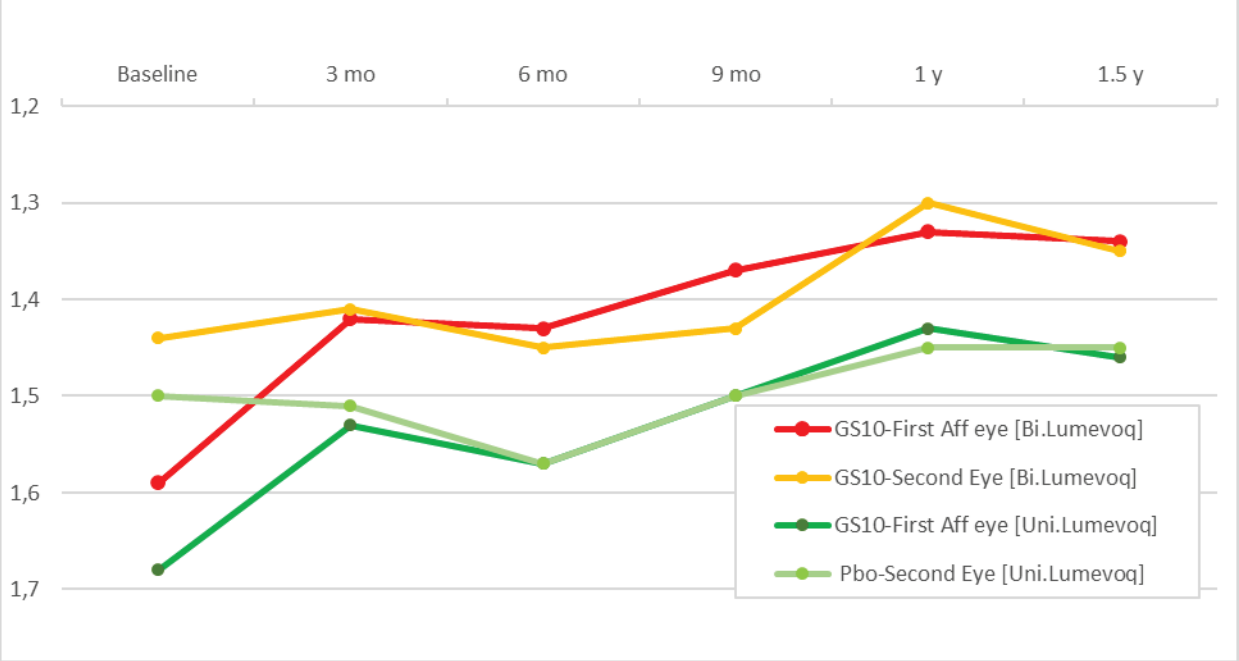
Figure 1. Best-Corrected Visual Acuity (BCVA) Change from Baseline (LogMAR) – Eye Groups



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

A dose effect, seen between bilaterally and unilaterally treated subjects, provides new evidence on LUMEVOQ® efficacy. In each group, the BCVAs of both eyes improved from baseline in tandem, but with a higher treatment effect for bilaterally treated subjects (Figure 2). The mean BCVA at 1.5 years for bilaterally and unilaterally treated subjects reached 1.35 and 1.45 LogMAR, respectively, with an absolute difference between arms of +5 letters in favor of bilaterally treated subjects.

Figure 2. Mean BCVA over time (LogMAR) – Eye Groups



Note: Mean LogMAR at each timepoint

Responder analyses show that most of the subjects responded to treatment and confirm that bilateral injections provide better efficacy. Most of the subjects had on-chart BCVAs at 1.5 year (able to read letters on a screen): 85% of bilaterally treated subjects and 72% of unilaterally treated subjects.

Efficacy demonstrated even more clearly in visual acuity improvement from nadir

Comparison against nadir (worst BCVA from baseline to 1.5 year) more starkly demonstrates the efficacy of LUMEVOQ®, even for the placebo eyes that showed the contralateral effect.

Table 2: Change in Best-Corrected Visual Acuity (BCVA) versus Nadir, 1.5 Years after Injection

	1st-affected eye	2nd-affected eye
Bilaterally injected subjects	LUMEVOQ **0.37 LogMAR** (**+19 ETDRS letters** equivalent; *p<0.0001****)	LUMEVOQ **0.31 LogMAR** (**+16 ETDRS letters** equivalent; *p<0.0001****)
Unilaterally injected subjects	LUMEVOQ **0.37 LogMAR** (**+19 ETDRS letters** equivalent; *p<0.0001****)	PLACEBO **0.25 LogMAR** (**+13 ETDRS letters** equivalent; *p<0.0001****)

At 1.5 years, improvement by at least 3 lines from nadir was demonstrated by 69% and 64% of bilaterally and unilaterally treated subjects, respectively.

Bilateral injections have favorable safety profile

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

LUMEVOQ® efficacy from the three Phase III trials – RESCUE, REVERSE and REFLECT – is highly consistent across the studies.

GenSight Biologics plans to add the full results of REFLECT to the EMA clinical dossier during the ongoing review of the LUMEVOQ® Marketing Authorisation Application and will present the analyses to the FDA later this year.

GenSight will host a KOL event on Friday, July 9, at 8:00 am EDT / 2:00 pm CEST, to present key results of REFLECT. Details will be announced at a later date.

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.

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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 800-1,200 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