

GenSight Biologics reports sustained efficacy and safety among LHON patients three years after LUMEVOQ® treatment

Paris, France, Monday, July 6, 2020, 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 that Leber Hereditary Optical Neuropathy (LHON) subjects treated with LUMEVOQ® experienced sustained efficacy and safety three years after a single injection with the gene therapy. These findings come from CLIN06, the long-term follow-up study to which participants in the RESCUE and REVERSE Phase III pivotal trials were invited.

These new data will reinforce GenSight Biologics' submission of LUMEVOQ® for marketing authorization in the European Union, which it intends to file in September 2020.

A total of 61 patients accepted the invitation to enroll in CLIN06 (30 from RESCUE and 31 from REVERSE), making CLIN06 one of the largest long-term follow-up studies for a rare disease treatment. The subjects were treated with LUMEVOQ® in one eye and with sham injection in the other.

At the start of the long-term follow-up, or at 2 years post-treatment, the subjects had already experienced an average gain of +18.8 letters equivalent* relative to the low point (their “nadir”**) of their visual acuity in their LUMEVOQ®-treated eyes and +17.3 letters equivalent in their sham-treated eyes. One year later, or three years after the one-time injection, the bilateral benefit was maintained, with LUMEVOQ®-treated eyes recording a mean improvement against nadir of +20.5 letters equivalent and sham-treated eyes demonstrating a mean improvement of +19.4 letters equivalent.

“CLIN06 demonstrates that the clinical improvement seen in prior LUMEVOQ studies is real and is maintained for 3 years post treatment,” commented **Dr. Mark L. Moster**, Neuro-Ophthalmology, Wills Eye Hospital, Professor of Neurology and Ophthalmology at Thomas Jefferson University, Philadelphia, PA, and Principal Investigator in the RESCUE, REVERSE and CLIN06 trials. “These results are far better than the natural history of LHON and provide further hope for improving the lives of our patients with this blinding disease.”

Table 1. BCVA Mean Improvement Vs. Nadir In LUMEVOQ® Long-Term Follow-Up (CLIN06)**

N = 61 subjects	Year 2 Post-Injection		Year 3 Post-Injection	
	LogMAR (Std Error)	Letters Equivalent*	LogMAR (Std Error)	Letters Equivalent*
LUMEVOQ®- treated eyes	-0.375 (0.3060)	+18.8	-0.410 (0.3650)	+20.5
Sham-treated eyes	-0.346 (0.2910)	+17.3	-0.387 (0.3690)	+19.4

Note: The CLIN06 sample consists of the RESCUE and REVERSE participants who accepted to be followed in the CLIN06 study.

Safety findings at 3-years were consistent with previous readouts, which concluded that LUMEVOQ® is well-tolerated: no serious adverse events were recorded among LUMEVOQ®-treated eyes, and no discontinuations occurred due to ocular events. There were no systemic serious adverse events or discontinuations related to study treatment or study procedure.

“By providing more proof of the durable and clinically meaningful efficacy of LUMEVOQ® along with its very high level of safety, these results highlight our gene therapy’s potential to treat patients with LHON and make a significant difference to their lives,” commented **Bernard Gilly**, Co-founder and Chief Executive Officer of GenSight. *“The data add further momentum to our plans to file for approval in Europe, which we intend to do with the utmost speed.”*

The pivotal trials RESCUE and REVERSE evaluated the efficacy and safety of a single intravitreal injection of LUMEVOQ® in patients at 0-6 months and 6-12 months, respectively, from onset of vision loss due to Leber Hereditary Optical Neuropathy (LHON) in subjects carrier of a mutated *ND4* mitochondrial gene.

To date, across clinical trials and cases of compassionate use, 194 patients have been treated with LUMEVOQ®, with many followed for at least 3 years post-injection. The dose used in LUMEVOQ® treatment, which introduces 9×10^{10} vg per eye, has been shown to result in negligible biodissemination.

*Assessments of best-corrected visual acuity (BCVA) were recorded in LogMAR. The change from nadir in LogMAR was converted to **“letters equivalent”** improvement by multiplying the LogMAR by -50 (ref. J.T. Holladay, J Refrac Surgery, 1997;13, 388-391).

****“Nadir”** is defined as the worst BCVA recorded in any of the visits in RESCUE, REVERSE and CLIN06, including the baseline visit immediately prior to the injection.

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About GenSight Biologics

GenSight Biologics S.A. is a clinical-stage biopharma company focused on discovering and developing 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, GS010, is in Phase III trials in Leber Hereditary Optic Neuropathy (LHON), a rare mitochondrial disease that leads to irreversible blindness in teens and young adults. 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 LUMEVOQ® (GS010)

LUMEVOQ® (GS010) 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 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 1,400 to 1,500 new patients who lose their sight every year in the United States and Europe.

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 will measure 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, will be used for statistical purposes. Both trials have been 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 will involve 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 will be 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 will include 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 are at 48, 72 and 96 weeks after injection.

The trials are 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 transferred to a long-term follow-up study that will last for three years.

ClinicalTrials.gov Identifiers:

REVERSE: NCT02652780

RESCUE: NCT02652767

About CLIN06 (RESCUE and REVERSE Long-term Follow-up)

CLIN06 is the long-term follow-up study of ND4 LHON subjects treated with LUMEVOQ® (GS010) gene therapy in the RESCUE or REVERSE Phase III Clinical Trials. The total study period for an individual subject is 3 years, i.e., 5 years post-gene therapy administration. No study treatment is administered during CLIN06.

The primary objective is to assess the long-term safety of intravitreal LUMEVOQ® administration up to 5 years post-treatment. The secondary objective is to assess the long-term treatment efficacy of the therapy and the quality of life (QoL) in subjects up to 5 years post-treatment. The first subject was enrolled on January 9, 2018. 61 subjects have enrolled.

ClinicalTrials.gov Identifiers:

CLIN06: NCT03406104