Press Release

GenSight Biologics Announces Publication of Indirect Comparison of LUMEVOQ® Versus Natural History in *ND4*-LHON Patients in Peer-Reviewed Journal *Ophthalmology and Therapy*

- Confirmed clinically significant and sustained improvement in visual acuity of 174 patients with Leber Hereditary Optic Neuropathy carrying the *ND4* mutation (*ND4*-LHON) treated with LUMEVOQ®
- 90% of eyes treated with LUMEVOQ® on-chart 4 years after their vision loss
- LUMEVOQ® continues to show promise as a novel therapy for the treatment of *ND4*-LHON

Paris, France, December 15, 2022, 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 the publication of a peer-reviewed article in the journal *Ophthalmology and Therapy* highlighting updated efficacy results from a pooled analysis of four Phase 3 studies showing an improvement in visual acuity in *ND4*-LHON patients treated with *lenadogene nolparvovec* (LUMEVOQ®).

The article, entitled *"Indirect Comparison of Lenadogene Nolparvovec Gene Therapy Versus Natural History in Patients with Leber Hereditary Optic Neuropathy Carrying the m.11778G>A MT-ND4 Mutation"*, incorporates data from the latest Phase 3 trial REFLECT, increasing the number of treated patients from 76 to 174 since the previously published pooled analysis. A group of 208 matched patients from natural history studies was used as an external control group.

The inclusion of REFLECT data permits outcomes in bilaterally treated eyes to be compared to those of patients treated unilaterally. When adjusted for covariates, the bilateral intravitreal injection (IVT) data presented in the article showed an improvement of +22.5 ETDRS letters versus natural history, as compared to an improvement of +17.5 ETDRS letters versus natural history for the unilateral IVT. Bilateral IVT also had an on-chart response rate of 79.2% compared to 67.0% for those with the unilateral IVT.

Overall, the patients with LUMEVOQ® showed a clinically significant and sustained improvement in their visual acuity when compared to the natural history patients. Mean improvement versus natural history was +15 ETDRS letters up to 3.9 years after treatment ($p<0.01$). At 4 years (48 months) after vision loss, the majority of treated eyes were on-chart compared to less than half of natural history eyes (89.6% versus 48.1%) ($p<0.01$). When adjusted for covariates of interest (gender, age of onset, ethnicity, and duration of follow-up), the estimated mean gain was - 0.43 logMAR (+ 21.5 ETDRS letters equivalent) versus natural history at last observation ($p<0.0001$). Thus, the treatment effect remained highly clinically significant when controlling for potential confounding factors (***figure 1***).

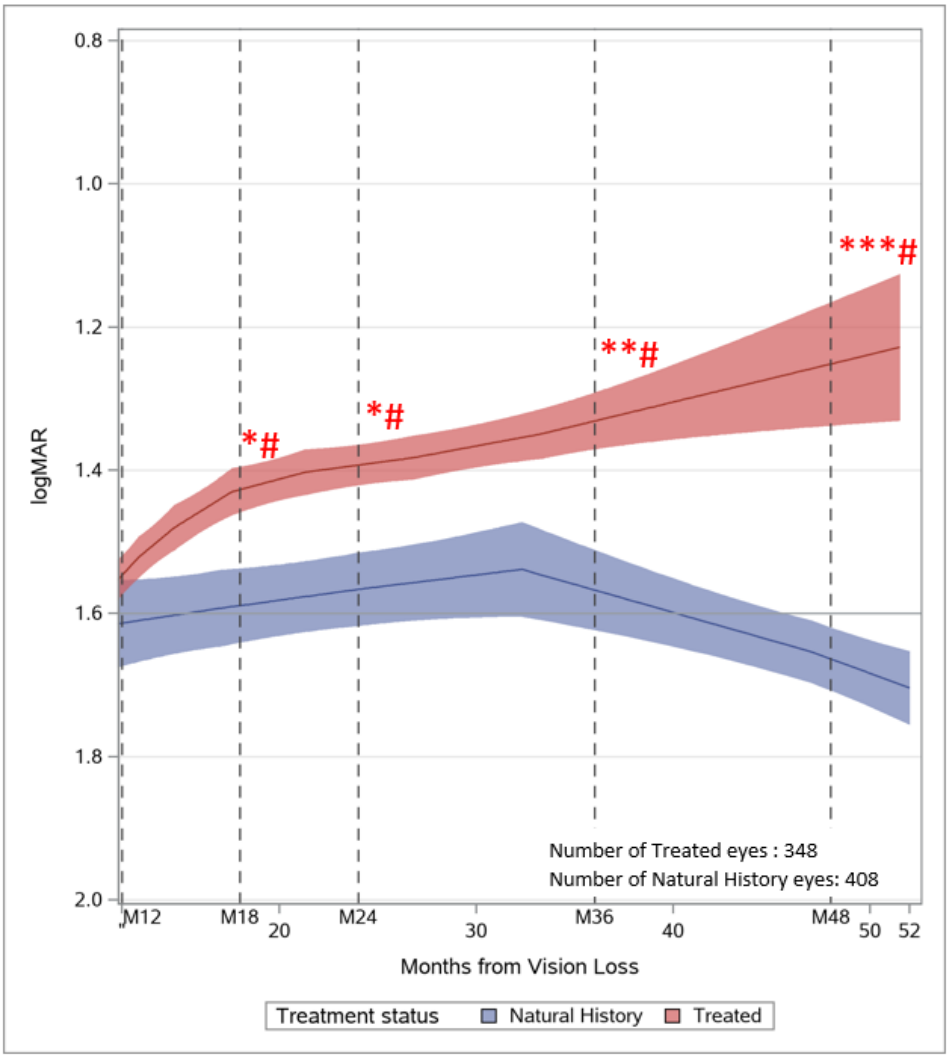
The evolution of natural history eyes showed an absence of recovery throughout the entire follow-up period, with a plateau up to 36 months followed by a slow decline. By contrast, eyes treated with LUMEVOQ® showed a progressive, continuous and sustained improvement between 12 and 52 months after vision loss.

"The results published in this peer-reviewed scientific paper provide more evidence of LUMEVOQ's potential as an effective treatment for LHON. The results indicate that LUMEVOQ treatment offers a better chance of recovery of vision than the published natural history of this disorder, giving hope to people affected by this debilitating blinding disease." said **Valerio Carelli,** MD, PhD, Professor of Medical Genetics, Director of the Program in Neurogenetics, Department of Biomedical and NeuroMotor Sciences, *University of Bologna School of Medicine* and lead author of the article.

The data was taken from four pooled Phase 3 studies, REVERSE, RESCUE and their long-term extension trial RESTORE, as well as the REFLECT trial. In the first three trials LUMEVOQ® was administered exclusively as a unilateral intravitreal injection (IVT), while in the REFLECT trial it was assessed as either an unilateral or a bilateral IVT.

The article is available in print and online via this link.

Figure 1: from Indirect Comparison of Lenadogene Nolparvovec Gene Therapy Versus Natural History in Patients with Leber Hereditary Optic Neuropathy Carrying the m.11778G>A MT-ND4 Mutation



*Note: Evolution of visual acuity of treated eyes versus natural history eyes. The evolution of visual acuities over time for treated eyes (n = 348) and natural history eyes (n = 408) was estimated by LOESS regression (solid line) with 95% CI around the fitted curve (shaded area). Visual acuity values > 52 months were assigned to the 52-month time point using the next observation carried backward method. Smoothing parameter: 0.315 for treated eyes and 0.408 for natural history eyes. The statistically significant difference between treated and natural history eyes is illustrated by the non-overlapping CIs of LOESS curves. Mean differences at month 18 [15; 21], month 24 [21; 30], month 36 [30; 42] and month 48 [42; 54] were estimated by a mixed-model ANCOVA with repeated measures: *P = 0.03, **P = 0.02 and ***P < 0.01 versus natural history; and with Kruskal Wallis test: #P < 0.01 versus natural history.*

Contacts

GenSight Biologics
Corporate Communications Director
Clothilde Caillet
ccaillet@gensight-biologics.com

RooneyPartners
Media Relations
Jeanene Timberlake
jtimberlake@rooneypartners.com
+1 646-770-8858

LifeSci Advisors
Investor Relations
Guillaume van Renterghem
gvanrenterghem@lifesciadvisors.com
+41 (0)76 735 01 31

Orpheon Finance
Retail Investors
James Palmer
j.palmer@orpheonfinance.com
+33 (0)7 60 92 77 74

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), is an investigational compound and has not been registered in any country at this stage; a marketing authorization application is currently under review by the EMA 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 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. LUMEVOQ® (GS010; lenadogene nolparvovec), is an investigational compound and has not been registered in any country at this stage; a marketing authorization application is currently under review by the EMA.

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