Press Release

GenSight Biologics reports sustained quality of life improvements at Week 72 of Phase III REVERSE clinical trial of GS010 for the treatment of Leber Hereditary Optic Neuropathy (LHON)

- Composite score and relevant sub-scores in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) showed sustained improvements at Week 48 and Week 72
- Magnitudes of score improvement observed with GS010 correlate with clinically meaningful improvements in best-corrected visual acuity (BCVA)

Paris, France, December 12, 2018, 7.30 am CET – 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 Week 72 analyses of the data from its Phase III REVERSE clinical trial revealed a sustained improvement in composite scores and selected sub-scores of a questionnaire used to measure patient perceptions of vision-related quality of life and ability to carry out daily activities impacted by loss of visual acuity. The REVERSE trial evaluates the safety and efficacy of a single intravitreal injection of GS010 (rAAV2/2-*ND4*) in 37 subjects whose visual loss due to 11778-*ND4* Leber Hereditary Optic Neuropathy (LHON) commenced between 6 and 12 months prior to study treatment.

All 37 patients in REVERSE were asked to complete the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), a reliable and valid vision-specific quality-of-life instrument that measures patients' perception of their ability to perform daily activities requiring high-acuity vision and their general sense of well-being. The test defines sub-scales for functions such as near-distance vision and vision-related dependency as well as measures of well-being such as ocular pain and vision-related mental health. These sub-scale scores are aggregated into a composite score, excluding the general health rating question.

Well-accepted as a source of patient-reported measures of vision-related function, the questionnaire has been used in many clinical trials. A study in neovascular AMD – which, like LHON, leads to loss of central vision – showed that a clinically meaningful 15-letter change in BCVA was associated with a 4- to 6-point change in the NEI VFQ-25 composite score and in sub-scores in three pre-specified areas (near activities, distance activities, and vision-specific dependency).

At Week 72, REVERSE patients reported mean improvement from baseline for NEI VFQ-25 scores in domains important to patients with loss of central vision: near activities, distance activities, vision-specific dependency and composite score. An improvement had already been observed at Week 48, confirming sustained enhancement of ability to perform activities of daily living. In addition, large improvements were also noted in other domains relevant to LHON patients: role difficulties, general vision, and overall mental health. Again, the improvements observed at Week 48 were sustained at Week 72. The relevant comparison in REVERSE is against patients' own baseline, because the NEI VFQ-25 is assessed by patient; by design, all REVERSE patients received an injection in one eye.

NEI VFQ-25 Results from REVERSE

Mean change from baseline (absolute score and percent)

	Composite Score**	Near Activities	Distance Activities	Dependency	Role Difficulties	General Vision	Mental Health
Week 48	+7.2 *23.2%*	+10.4 *65.1%*	+9.6 *49.8%*	+12.4 *100.6%*	+14.5 *65.0%*	+10.3 *50.9%*	+11.2 *81.9%*
Week 72	+8.1 *25.2%*	+9.5 *58.1%*	+8.2 *42.5%*	+18.9 *130.2%*	+15.2 *70.9%*	+11.9 *54.1%*	+15.2 *105.6%*
Clinically relevant difference*	+3.90 to +4.34	+4.67 to +6.06	+5.15 to +5.38	+4.72 to +4.98	+3.31 to +4.70	+4.38 to +4.82	+4.70 to +4.88

*****Suñer *et al.* (2009): clinically relevant score differences based on a clinically significant 15-letter BCVA improvement at 12 months.
**The composite score is an average of the vision-targeted sub-scale scores, excluding the general health rating question.

Improvement from baseline at Week 72 for other sub-scales: social functioning: +2.4 (23.3%); ocular pain: +1.4 (5.6%); color vision: +5.6 (20.8%); peripheral vision: +1.4 (15.5%). Missing values for general health subscale. Driving questions not pertinent to LHON patients.

"It is heartening and exciting to see the NEI VFQ-25 corroborate the effects that have been demonstrated by GS010: relative protection of retinal ganglion cells and their axons, as well as visual function improvement," commented **Bernard Gilly**, Co-founder and Chief Executive Officer of GenSight. *"This tells us that clinical measurements obtained by our investigators add up to patients feeling that they can function better in day-to-day activities."*

Dr. Mark Moster, Neuro-Ophthalmology, Wills Eye Hospital; Professor of Neurology and Ophthalmology at Thomas Jefferson University, Philadelphia, PA; and Principal Investigator in the REVERSE, RESCUE, and REFLECT trials, concurred. "In the final analysis, improvement in quality of life measures is perhaps the most compelling metric of therapeutic intervention," he said. "Although it is important for clinicians to find objective improvements in specific visual functions, it is even more important that we improve the quality of life of our patients rather than any one objective measure of vision. These results offer demonstration of that successful outcome."

As per protocol, REVERSE subjects will be evaluated again at 96 weeks, and data will be reported in the second quarter of 2019.

Topline 48-week data for RESCUE, the second Phase III clinical trial of GS010 in the treatment of LHON, is expected in early Q1 2019.

Reference cited: Suñer *et al*., *Invest Ophthalmol Vis Sci.* 2009;50:3629–3635. DOI:10.1167/iovs.08-3225

On the VFQ-25: The National Eye Institute (NEI) sponsored the development of the VFQ-25, which aims to measure the influence of visual disability and visual symptoms on generic health domains and task-oriented domains related to daily visual functioning. The survey consists of a base set of vision-targeted questions that represent 11 vision-related constructs (domains), plus an additional single-item general health rating question. Respondents use numerical scales to rate their difficulty in performing vision-dependent activities and to assess their well-being. For example, "near activities", referring to "difficulty with near vision activities", encompasses activities such as "doing work or hobbies that require [the respondent] to see well up close, such as cooking, sewing, fixing…" and "finding something on a crowded shelf". The numerical scores are converted to a 0-to-100 scale, with higher scores representing better functioning. The sub-scale scores within a domain are averaged to create the domain sub-scale score. The composite score is a simple average of the domain sub-scale scores, excluding the general health rating question.

Contacts

GenSight Biologics
Thomas Gidoin
Chief Financial Officer
tgidoin@gensight-biologics.com
+33 (0)1 76 21 72 20

RooneyPartners
Media Relations
Marion Janic
mjanic@rooneyco.com
+1-212-223-4017

The Trout Group
US Investor Relations
Chad Rubin
crubin@troutgroup.com
+1-646-378-2947

James Palmer
Europe Investor Relations
j.palmer@orpheonfinance.com
+33 7 60 92 77 74

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 GS010

GS010 targets Leber Hereditary Optic Neuropathy (LHON) by leveraging a mitochondrial targeting sequence (MTS) proprietary technology platform, arising from research works 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.

About RESCUE and REVERSE

RESCUE and REVERSE are two separate randomized, double-masked, sham-controlled pivotal 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 sham-treated 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.

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. Topline results of RESCUE at 48 weeks are expected in early Q1 2019.

ClinicalTrials.gov Identifiers:
REVERSE: NCT02652780
RESCUE: NCT02652767