Press Release

GenSight Biologics reports positive additional data from REVERSE Phase III clinical trial of GS010 for treatment of Leber Hereditary Optic Neuropathy (LHON)

- Clinically meaningful bilateral improvement of visual acuity supersedes observed and published natural evolution of the disease
- Bilateral improvement is not consistent with a placebo effect
- Statistically significant preservation of both retinal ganglion cells and temporal retinal nerve fiber layer in GS010-treated eyes vs. sham-treated eyes objectively demonstrate protective effect of GS010
- *Post hoc* trends point to larger benefit in subjects at a less advanced stage of LHON
- Findings to be discussed in a KOL event in NYC today *(live webcast and replay)*

Paris, France, June 12, 2018, 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 additional results from the REVERSE Phase III clinical trial evaluating 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.

Topline results, reported in April, showed that the clinically significant improvement of +11 ETDRS letters (-0.218 logMar) in GS010-treated eyes was matched by an unexpected improvement of +10 ETDRS letters (-0.211 LogMAR) in the sham-treated eyes. This caused the study not to meet its primary endpoint predefined as a +15 ETDRS letters difference in visual acuity between GS010- and sham-treated eyes.

At the same time, the study successfully met secondary endpoints defined by Spectral-Domain Optical Coherence Tomography (SD-OCT) parameters, specifically the change in ganglion cell layer macular volume measured from baseline to week 48 and change in thickness of the temporal quadrant of the retinal nerve fiber layer from baseline to week 48. These results demonstrated a direct biologic and physiological impact of GS010 on the anatomy relevant to LHON.

Further analyses now demonstrate that, although some secondary endpoints did not show significant or meaningful changes, **contrast sensitivity as determined by Pelli-Robson low-vision testing almost doubled in the GS010-treated eyes compared to sham-treated eyes**. GS010-treated eyes started with lower contrast sensitivity (0.25 LogCS on average) than sham-treated eyes (0.35 LogCs on average). At week 48, GS010-treated eyes gained on average +0.20 LogCS, and the contrast sensitivity in sham-treated eyes remained stable (+0.08 LogCS on average).

As per protocol, all 37 subjects will be evaluated again at 96 weeks, and data will be reported in the first quarter of 2019.

In addition, *post hoc* analyses revealed trends that suggest GS010 may have a larger positive impact on the visual acuity of patients at relatively less advanced or severe stages of the disease:

- **Subjects who entered study with better vision (on-chart eyes) tended to have better clinical outcomes.** At week 48, in on-chart best-seeing eyes, GS010-treated eyes gained on average +12 ETDRS letters (-0.236 LogMAR) compared to +4 ETDRS letters (-0.075 LogMAR) in sham-treated eyes.

- **Subjects whose vision loss was less than 9 months tended to have better clinical outcomes.** 75% of GS010-treated eyes that showed a trend in visual acuity improvement at week 48 had vision loss for less than 9 months at time of treatment administration.

- **Subjects who were younger (< 21 years) at enrollment tended to have better clinical outcomes**

"Examining the totality of the data, the REVERSE results suggest a therapy that may provide meaningful bilateral improvement of vision for our subjects, which is not what would be expected from the natural history of this disease. Our planned follow-up of REVERSE subjects will enable us to monitor the observed continuous bilateral improvement after another year," remarked **Dr. Barrett Katz**, Chief Medical Officer of GenSight. *"GS010 treated eyes were significantly more likely to achieve vision of 20/200 or better when compared to sham treated eyes. In addition, trends suggest a potentially larger benefit for subjects at earlier stages of LHON. We eagerly await what data from the RESCUE trial will show."*

"Although the clinically meaningful bilateral improvement of visual acuity observed in most subjects remains to be further explained, it is undoubtedly a wonderful outcome for patients and their families," commented **Bernard Gilly**, Chief Executive Officer of GenSight. *"We are now going to discuss the full results with regulatory authorities so that we are aligned on how best to bring GS010 to market with our existing Phase III program within our defined timelines."*

The full set of data and *post hoc* findings will be presented and discussed at a Key Opinion Leader (KOL) Event today in New York City from 8.30 a.m. – 11:00 a.m. EST. Medical experts, consisting of specialists who were investigators in the trial and key opinion leaders in neuro-ophthalmology and ophthalmology, will introduce LHON and its natural history, present the findings and discuss their significance in a panel discussion. Lissa Poincenot, a leading patient advocate, will present her perspectives on what the results mean for patients and their caregivers. To conclude the session, Bernard Gilly will share the company's regulatory strategy and upcoming consultations with the FDA and EMA to remain on track with its goal of submitting dossiers as planned in Q2 2019.

The presentation will be webcast live at https://www.gensight-biologics.com/2018/05/21/gensight-biologics-to-host-kol-event-on-june-12-2018/. Participants attending in person or on the webcast will have the opportunity to pose questions. For those not available to attend or listen to the live broadcast, a replay will be archived for 3 months and available on the Company's website.

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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 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 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 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 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.

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 Q3 2018.

ClinicalTrials.gov Identifiers:
REVERSE: NCT02652780
RESCUE: NCT02652767

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.

The trial is planned to enroll 90 patients with vision loss up to 1 year in duration, and will be conducted in multiple centers in Europe and in the US.

In the active arm, GS010 will be administered as a single intravitreal injection to both eyes of each subject. In the placebo arm, GS010 will be administered as a single intravitreal injection to the first affected eye, while the fellow eye will receive a placebo injection.

The primary endpoint for the REFLECT trial is the BCVA reported in LogMAR at 1-Year 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 will be 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, color and contrast sensitivity and quality of life scales. The first subject was treated in March 2018.

ClinicalTrials.gov Identifiers:
REFLECT: NCT03293524