Press Release

GenSight Biologics completes enrollment of GS010 REFLECT Phase III trial in the treatment of Leber Hereditary Optic Neuropathy ahead of schedule

Paris, France, July 11, 2019, 5.45 pm 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 announced that enrollment in REFLECT, a Phase III clinical trial of GS010 for the treatment of Leber Hereditary Optic Neuropathy (LHON), was successfully completed ahead of schedule.

REFLECT is a multi-center, randomized, double-masked, placebo-controlled study to evaluate the efficacy and safety of bilateral injections of GS010 in subjects with LHON due to the NADH dehydrogenase 4 (ND4) mutation. Enrolling the target number of 90 subjects was originally anticipated to be completed in September 2019; instead the 98th subject enrolled in the trial was treated on July 2.

"The conclusion of enrollment for the REFLECT study is a milestone in the story of gene therapy for Leber Hereditary Optic Neuropathy," commented **Nancy J. Newman, MD**, LeoDelle Jolley Professor of Ophthalmology and Neurology, Emory University School of Medicine, Atlanta, USA, and Principal Investigator in REFLECT. *"The recruitment of nearly 100 patients in less than two years is a tribute to the support of the LHON community in this partnership among researchers, clinicians and patients trying to bring therapy and hope to this blinding disease."*

The trial was designed and agreed under a Special Protocol Assessment (SPA) with the Food and Drug Administration (FDA) in the United States but is not required for the Marketing Authorization Application (MAA) in the European Union, RESCUE and REVERSE being considered by the EMA as pivotal for filing in the EU. The trial enrolled subjects with vision loss up to 1 year in duration and is underway across multiple centers in the United States, Europe, and Taiwan. In the active arm, GS010 was administered as a single intravitreal injection to both eyes 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 best corrected visual acuity (BCVA) change from baseline reported in LogMAR at 52 weeks post-treatment in the second affected/not yet affected eye. 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, contrast sensitivity and quality of life.

The first subject was treated in March 2018; topline Week 52 results are expected to be available in the third quarter of 2020.

GS010 has Orphan Drug Designation both in the United States and in Europe.

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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 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 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 are expected in 2019 for both trials, after which patients will be transferred to a long-term follow-up study that will last for three years.

ClinicalTrials.gov Identifiers:
REVERSE: NCT02652780
RESCUE: NCT02652767

About REFLECT

REFLECT is a multi-center, randomized, double-masked, placebo-controlled study to evaluate the efficacy and safety of bilateral injections of GS010 in subjects with LHON due to the NADH dehydrogenase 4 (*ND4*) mutation.

The trial enrolled 98 subjects with vision loss up to 1 year in duration and is conducted in multiple centers in Europe, in the US and in Taiwan.

In the active arm, GS010 was administered as a single intravitreal injection to both eyes 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-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. 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 first subject was treated in March 2018; topline Week 52 results are expected to be available in the third quarter of 2020.

ClinicalTrials.gov Identifiers:
REFLECT: NCT03293524