Sio Gene Therapies Announces Positive Six-Month Follow-Up Data from Low-Dose Cohort of Phase 1/2 Trial of AXO-AAV-GM1 for GM1 Gangliosidosis

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- Generally well-tolerated with a favorable safety profile in five patients
- Serum beta-galactosidase enzyme activity increased in all patients at all timepoints between Day 7 and Month 6, representing an approximate doubling in enzyme activity after gene transfer
- At Month 6, enzyme activity restored to 23-57% (mean: 38%) of normal reference levels
- All five children demonstrated signs of clinical disease stability as assessed by Vineland-3 Growth Scale Value, Upright and Floor Mobility, and Clinical Global Impression (CGI) scales
- High-dose cohort initiated in November 2020; two patients now dosed without complications

NEW YORK and RESEARCH TRIANGLE PARK, N.C., Dec. 15, 2020 (GLOBE NEWSWIRE) -- Sio Gene Therapies Inc. (NASDAQ: SIOX), a clinical-stage company focused on developing gene therapies to radically improve the lives of patients with neurodegenerative diseases, today reported positive six-month follow-up data from the low-dose cohort ($1.5x10^{13}$ vg/kg) of the Company's dose escalation study of AXO-AAV-GM1, its adeno-associated viral vector (AAV)9-based gene therapy candidate for the treatment of GM1 gangliosidosis. Initial data from the ongoing Phase 1/2 study in five patients in the low-dose cohort showed that AXO-AAV-GM1 was generally well tolerated with a favorable safety profile and provide early indications of clinical disease stability.

"We are excited to report encouraging safety, tolerability, biomarker, and preliminary efficacy data for AXO-AAV-GM1, the first gene therapy evaluated in a clinical trial for GM1 gangliosidosis, a life-limiting disease caused by mutations in the *GLB1* gene that impair beta-galactosidase enzyme activity. Safety was the key measure in this first-in-human study, and we are pleased to see a favorable safety profile in the first five children treated with the low-dose," said Gavin Corcoran, M.D., Chief R&D Officer of Sio Gene Therapies. "At this early timepoint post-treatment, we observed an increase in beta-galactosidase enzymatic activity, reaching on average 38% of normal reference levels. This is encouraging given that evidence in the medical literature for lysosomal storage diseases suggests that increases in enzyme activity, to between 10-20% of normal levels, can lead to clearance of stored lysosomal substrates and may be associated with slower disease progression. We are also encouraged by consistent signs of disease stabilization across multiple measures of neurodevelopment in all five children at six months as compared to the predictable decline observed in natural history studies. These data highlight the potential for the investigational gene therapy to treat the underlying genetic cause of this disease, preserve functional outcomes, and reduce disease burden for patients and their families. Further, the safety profile observed in the low-dose cohort support moving forward with the high-dose cohort of AXO-AAV-GM1 in the ongoing Phase 1/2 study. We look forward to presenting program updates at future medical conferences."

Dr. Cynthia Tifft, Deputy Clinical Director of the National Human Genome Research Institute (NHGRI) added, "I have been studying and caring for children with GM1 gangliosidosis for more than 10 years, and I have seen the impact of this relentlessly progressive, uniformly fatal disease on the children and the heavy physical and psychological burden on families and caregivers. With no approved therapies, the treatment options today are limited to aggressive supportive care with physical, occupational and speech therapy and later with feeding tubes and anti-convulsants to minimize seizures. I am encouraged by the results-to-date where we have seen preservation of function and in a few measures even improvement. As we advance to the high-dose cohort, I am also pleased that the side effects of the treatment have been minimal and easily managed."

Six-Month Follow-Up Results

Baseline Characteristics:

- Total of 5 Type II patients evaluated: 4 late-infantile onset patients (aged 32-68 months at time of dosing**)**, and 1 juvenile onset patient (aged 45 months at time of dosing).
- All patients had documented biallelic mutations in *GLB1* gene, deficiency of beta-galactosidase enzyme activity, and clinical phenotype consistent with GM1 gangliosidosis.
- All 5 patients exhibited impairment of fine motor skills and change in walking pattern on clinical history at baseline.

Safety and Tolerability:

- AXO-AAV-GM1 was generally well-tolerated with a favorable safety profile at the low dose ($1.5x10^{13}$ vg/kg) delivered intravenously.
- There have been no serious adverse events (SAEs) related to gene therapy.
    - One SAE was described: a single patient experienced bacterial sepsis due to a PICC line infection, which was considered to be unrelated to the investigational drug product, and which resolved within a few days following line removal and administration of IV antibiotics.
- The most common adverse events were considered mild to moderate. Transient AST elevations were observed in 4 subjects, none of which required clinical intervention or had associated clinical sequelae. There were no other adverse events indicative of impaired liver function including serum bilirubin, GGT, and ALT. No clinically relevant changes were

observed in platelet count.
- The favorable safety profile in the low-dose cohort supports continued enrollment of patients in the high-dose cohort ($4.5x10^{13}$ vg/kg), in which two patients have now been dosed without complications.

Biomarkers:

- Serum beta-galactosidase enzyme activity was sampled at nine distinct timepoints between Day 7 and Month 6, and increased from baseline between 71-138% (mean: 110%) during the 6-month observation period, representing an approximate doubling in enzyme activity after gene transfer. At Month 6, serum enzyme activity increased by an average of 71% from baseline (range: 33%-127%) across the five patients.
- On average, serum enzyme activity was restored to 38% of normal reference levels at Month 6, with individual patients ranging from 23-57% of normal reference levels. The reference level was defined by the lowest level of enzyme activity in serum from 30 healthy adult volunteers using the same validated assay of beta-galactosidase enzyme activity as was used to assess the patients in the study.
- Cerebrospinal fluid (CSF) samples were collected from all patients through lumbar puncture. Development and validation of biomarker assays for CSF is currently ongoing.

Clinical and Functional Outcomes:

- Patients were assessed by multiple measures of neurodevelopment including the Vineland Adaptive Behavior Scales 3rd Edition (VABS-3), Upright and Floor Mobility Score, and Clinical Global Impression (CGI).
    - VABS-3 is a standardized measure of adaptive behavior that is widely used to evaluate communication, daily living, social skills, and motor function. VABS-3 scores have a predictable relationship to ability, allowing for comparative assessments with increasing age.
    - Predictable functional decline in abilities has been well documented in natural history studies, showing an age-related statistically significant decline in all sub-domains of the VABS-3 scale and in Floor and Upright Mobility Scores.
- All five patients demonstrated disease stability at 6 months post-treatment as assessed by VABS-3 Growth Scale Value scores, Upright and Floor Mobility Score, and CGI relative to baseline values.
- Subdomain Growth Scale Value scores in the VABS-3 remained stable or improved in four out of five patients.
- Floor Mobility Scores were scored at the highest level based on age in all five patients, indicating the ability to crawl in 4-points independently, and remained stable at all timepoints evaluated over the six-month observation period.
- Upright Mobility Scores were stable in all five patients, with function maintained at all timepoints evaluated over the 6-month observation period.
- Clinical Global Impression (CGI), a clinician's assessment of change in disease severity from baseline, mildly improved in four out of five patients and remained stable in the fifth patient over the six-month evaluation period.
- Additional data will be collected at the 12-month evaluation including several measures of the systemic manifestations of GM1 gangliosidosis.

The Phase 1/2 study (NCT03952637) is designed to evaluate the safety, tolerability, and potential efficacy of AXO-AAV-GM1 delivered intravenously in children with Type I and Type II GM1 gangliosidosis. In Stage 1 of the study, the low-dose cohort is evaluating $1.5x10^{13}$ vg/kg AXO-AAV-GM1 gene therapy in a total of five Type II (late-infantile and juvenile) patients, and the ongoing high-dose cohort is evaluating a dose of $4.5x10^{13}$ vg/kg AXO-AAV-GM1 gene therapy in both Type I (early infantile) and Type II children.

About AXO-AAV-GM1

AXO-AAV-GM1 delivers a functional copy of the *GLB1* gene via an adeno-associated viral (AAV) vector, with the goal of restoring β-galactosidase enzyme activity for the treatment of GM1 gangliosidosis. The gene therapy is delivered intravenously, which has the potential to broadly transduce the central nervous system and treat peripheral manifestations of the disease as well. Preclinical studies in murine and a naturally-occurring feline model of GM1 gangliosidosis have supported AXO-AAV-GM1's ability to improve β-galactosidase enzyme activity, reduce GM1 ganglioside accumulation, improve neuromuscular function, and extend survival.

AXO-AAV-GM1 has received both Orphan Drug Designation and Rare Pediatric Disease Designation from the Food and Drug Administration and is the only gene therapy in clinical development for both Type I and Type II GM1 gangliosidosis.

In 2018, Sio licensed exclusive worldwide rights from the University of Massachusetts Medical School for the development and commercialization of gene therapy programs for GM1 gangliosidosis and GM2 gangliosidosis, including Tay-Sachs and Sandhoff diseases.

About Sio Gene Therapies

Sio Gene Therapies combines cutting-edge science with bold imagination to develop genetic medicines that aim to radically improve the lives of patients. Our current pipeline of clinical-stage candidates includes the first potentially curative AAV-based gene therapies for GM1 gangliosidosis and Tay-Sachs/Sandhoff diseases, which are rare and uniformly fatal pediatric conditions caused by single gene deficiencies. We are also expanding the reach of gene therapy to highly prevalent conditions such as Parkinson's disease, which affects millions of patients globally. Led by an experienced team of gene therapy development experts, and supported by collaborations with premier academic, industry and patient advocacy organizations, Sio is focused on accelerating its candidates through clinical trials to liberate patients with debilitating diseases through the transformational power of gene therapies. For more information, visit www.siogtx.com.

Forward-Looking Statements

This press release contains forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “will,” “expect,” “believe,” “estimate,” and other similar expressions are intended to identify forward-looking statements. For example, all statements Sio makes regarding costs associated with its operating activities are forward-looking. All forward-looking statements are based on estimates and assumptions by Sio’s management that, although Sio believes to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Sio expected. Such risks and uncertainties include, among others, the impact of the Covid-19 pandemic on our operations, the initiation and conduct of preclinical studies and clinical trials; the availability of data from clinical trials; the development of a suspension-based manufacturing process for AXO-Lenti-PD; the scaling up of manufacturing, the expectations for regulatory submissions and approvals; the continued development of our gene therapy product candidates and platforms; Sio’s scientific approach and general development progress; and the availability or commercial potential of Sio’s product candidates. These statements are also subject to a number of material risks and uncertainties that are described in Sio’s most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission on November 13, 2020, as updated by its subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. Sio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

Contacts:

Media

Josephine Belluardo, Ph.D.
LifeSci Communications
(646) 751-4361
jo@lifescicomms.com
info@siogtx.com

Investors and Analysts

David Nassif
Sio Gene Therapies Inc.
Chief Financial Officer and General Counsel
(646) 677-6770
investors@siogtx.com

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