MeiraGTx Announces Publication of New Research Identifying Underlying Mechanism of Functional Improvement Seen with AAV-GAD Gene Therapy in Parkinson's Disease

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Findings Published in *Science Translational Medicine* Show AAV-GAD Exerts Clinical Benefits by Inducing the Formation of New Brain Pathways

Results Expand on Findings from Completed Phase 2 Clinical Trial

LONDON and NEW YORK, Dec. 12, 2018 (GLOBE NEWSWIRE) -- MeiraGTx Holdings plc (NASDAQ:MGTX), a vertically integrated, clinical stage gene therapy company, today announced publication of research assessing the mechanism underlying the motor improvement observed in patients with Parkinson's disease who were treated with adeno-associated virus (AAV) encoding glutamic acid decarboxylase (AAV-GAD), an investigational gene therapy product candidate, in a completed Phase 2 study. In the new research, which was published in the November 28, 2018 issue of *Science Translational Medicine,* patients treated with AAV2-GAD gene therapy (in which glutamic acid decarboxylase [GAD] was delivered into the subthalamic nucleus [STN]) expressed a distinct treatment-related metabolic brain network, providing a clinical benefit by inducing the formation of new polysynaptic pathways connecting the STN to cortical motor regions. Rather than act through conventional motor pathways involving certain regions of the brain, AAV-GAD gene therapy was observed to co-opt adjacent "nonmotor" regions in the treated patients.

The publication, titled "Gene therapy reduces Parkinson's disease symptoms by reorganizing functional brain connectivity," can be accessed here.

"These new research findings provide important information about the mechanism of action of AAV-GAD and support its potential benefit in patients with Parkinson's disease, who currently are limited to symptomatic treatments that do not modify the underlying disease process. The research also suggests that visualization of treatment-induced brain circuits can be useful in clinical trials in identifying treatment responses and providing insight into underlying biological mechanisms," said Alexandria Forbes, Ph.D., president and chief executive officer of MeiraGTx. "We believe our novel gene therapy product candidate could potentially transform the treatment of Parkinson's disease patients."

The Phase 2 study of AAV-GAD was the first successful randomized, double-blind, sham-controlled trial of its kind for a gene therapy product candidate targeting a brain disorder. Results were published in *The Lancet Neurology* in March 2011.[i]

To understand the effects of AAV-GAD therapy, a team of scientists from the Center for Neurosciences at The Feinstein Institute for Medical Research, the Institute for Diabetes, Obesity and Metabolism at the Perelman School of Medicine and other organizations analyzed metabolic imaging data (PET imaging) from patients in the Phase 2 clinical trial who received gene therapy and those randomized to sham surgery. In the Phase 2 trial, all of the patients had undergone metabolic brain imaging at baseline and at 6 and 12 months post-operatively, and those treated with AAV-GAD showed clinical improvement at 6 and 12 months compared with sham controls ($p<0.04$).

The research published in *Science Translational Medicine* showed that patients treated with AAV-GAD gene therapy developed a unique treatment-dependent metabolic brain network (termed the GAD-related pattern or GADRP), which reflected the formation of new functional pathways linking the STN to motor cortical regions. GADRP was characterized by increased metabolism in certain brain regions (i.e., the premotor region extending into the adjacent motor cortex and the supramarginal gyrus) along with relatively reduced metabolic activity in other brain regions (i.e., the thalamus, the caudate, the putamen/globus pallidus and the inferior frontal gyrus). The research also showed that the GADRP correlated with clinical improvement in the gene therapy-treated subjects as measured by changes in the Unified Parkinson's Disease Rating Scale (UPDRS) motor ratings ($p<0.009$). In contrast, the clinical correlation with sham surgery-related pattern was not significant ($p=0.48$).

About AAV-GAD
AAV-GAD is an investigational gene therapy medicine designed to deliver the GAD gene to the STN in order to increase production of GABA, the primary inhibitory neurotransmitter in the human brain. GAD is the rate-limiting enzyme in the synthesis of GABA. Therefore, it is believed that increasing subthalamic nucleus GAD expression through gene therapy will result in normalization of motor circuits and improve symptoms in Parkinson's disease patients without affecting other brain regions that can be responsible for complications associated with existing therapies.

AAV-GAD has received Fast Track designation from the U.S. Food and Drug Administration (FDA).

About the Phase 2 Study of AAV-GAD
The Phase 2 study included 45 patients with medically refractory Parkinson's disease who were randomized 1:1 to receive either AAV-GAD gene therapy delivered by injection into the STN on both sides of the brain or bilateral sham surgery. Subjects were followed for one year, and all results remained blinded until the final treated patient reached the 6-month primary endpoint. The trial met the pre-specified, per-protocol primary endpoint, with a significant improvement in the off-medication motor section of the UPDRS part 3 compared to baseline. There was also a significant difference in the degree of improvement compared with patients in the sham arm. Other endpoints also showed significant improvements in AAV-GAD treated patients compared to patients in the sham arm.

In the study, AAV-GAD was well tolerated. No significant adverse events related to the therapy and no speech or cognitive complications were observed. The most commonly reported adverse events were transient mild or moderate headache (7 in treated arm vs. 2 in sham arm), nausea (6 in treated arm vs. 2 in sham arm) and worsening of Parkinson's disease (0 in treated arm vs. 8 in sham arm).

About Parkinson's Disease
Parkinson's disease affects nearly 1 million Americans and 10 million people worldwide. Each year, 60,000 new cases of Parkinson's disease are diagnosed in the United States, where it is the second most common neurodegenerative disease after Alzheimer's disease and the 14 th leading cause

of death. Parkinson's disease is associated with a progressive loss of motor control (e.g., shaking or tremor at rest and lack of facial expression), as well as non-motor symptoms (e.g., depression and anxiety). There is no cure for Parkinson's disease.

About MeiraGTx
(NASDAQ:MGTX) is a vertically integrated, clinical stage gene therapy company with four ongoing clinical programs and a broad pipeline of preclinical and research programs. MeiraGTx has core capabilities in viral vector design and optimization and gene therapy manufacturing, as well as a potentially transformative gene regulation technology. Led by an experienced management team, MeiraGTx has taken a portfolio approach by licensing, acquiring and developing technologies that give depth across both product candidates and indications. MeiraGTx's initial focus is on three distinct areas of unmet medical need: inherited retinal diseases, severe forms of xerostomia and neurodegenerative diseases. Though initially focusing on the eye, salivary gland and central nervous system, MeiraGTx intends to expand its focus in the future to develop additional gene therapy product candidates for patients suffering from a range of serious diseases.

For more information, please visit www.meiragtx.com.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding product candidate development, growth expectations or efficacy, as well as statements that include the words "expect," "intend," "plan," "believe," "project," "forecast," "estimate," "may," "should," "anticipate" and similar statements of a future or forward-looking nature. These forward-looking statements are based on management's current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, our incurrence of significant losses; any inability to achieve or maintain profitability, acquire additional capital, identify additional and develop existing product candidates, continue operating as a going concern, successfully execute strategic priorities, bring product candidates to market, build-out the manufacturing facility and processes, successfully enroll patients in and complete clinical trials, accurately predict growth assumptions, recognize benefits of any orphan drug designations, retain key personnel or attract qualified employees, or incur expected levels of operating expenses; failure of early data to predict eventual outcomes; failure to obtain FDA or other regulatory approval for product candidates within expected time frames or at all; the novel nature and impact of negative public opinion of gene therapy; failure to comply with ongoing regulatory obligations; contamination or shortage of raw materials; changes in healthcare laws; risks associated with our international operations; significant competition in the pharmaceutical and biotechnology industries; dependence on third parties; risks related to intellectual property; litigation risks; and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2018 filed with the U.S. Securities and Exchange Commission ("SEC"), as such factors may be updated from time to time in our other filings with the SEC, which are accessible on the SEC's website at www.sec.gov. These and other important factors could cause actual results to differ materially from those indicated by the forward-looking statements made in this press release. Any such forward-looking statements represent management's estimates as of the date of this press release. While we may elect to update such forward-looking statements at some point in the future, unless required by law, we disclaim any obligation to do so, even if subsequent events cause our views to change. Thus, one should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this press release.

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[i] LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW et al. AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol.* 2011;10:309-319.

Source: MeiraGTx