Taysha Gene Therapies Announces Publication of Preclinical Data for TSHA-102 in Rett Syndrome in Brain, a Highly Esteemed Neurological Science Peer-Reviewed Journal

May 10, 2021

Preclinical data provide quantitative evidence of miRARE's ability to exhibit genotype-dependent regulation of MECP2 gene expression across different brain regions in both wild type and knockout mouse models of Rett syndrome

TSHA-102 resulted in a statistically significant survival extension by 56% in 4-5-week-old knockout Rett mice with meaningful accumulated disease whereas unregulated constructs did not extend survival significantly in the validated MECP2 knockout Rett mouse model

Significant survival benefit in 4-5-week-old TSHA-102-treated knockout Rett mice with meaningful accumulated disease a more translatable model of the disorder in humans

These quantitative data, for the first time, demonstrated miRARE's ability to regulate gene expression on a cell-by-cell basis, highlighting its potential application in numerous dose-sensitive diseases

Data support an IND/CTA filing for TSHA-102 in Rett syndrome in the second half of 2021, with initiation of a Phase 1/2 trial anticipated by year-end

Estimated 25,000 patients in U.S. and Europe represent multi-billion-dollar commercial opportunity

DALLAS--(BUSINESS WIRE)--May 10, 2021-- Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a patient-centric, pivotal-stage gene therapy company focused on developing and commercializing AAV-based gene therapies for the treatment of monogenic diseases of the central nervous system (CNS) in both rare and large patient populations, today announced the publication of new preclinical data for TSHA-102 in Rett syndrome. The data were published online and will be included in the May edition of *Brain*, a highly esteemed neurological science peer-reviewed journal.

"Effective gene therapy targeting *MECP2* for the treatment of Rett syndrome has been elusive due to the inability to properly regulate transgene expression," said Steven Gray, Ph.D., Chief Scientific Advisor at Taysha and Associate Professor in the Department of Pediatrics at UT Southwestern. "The built-in self-regulatory feedback loop mechanism in TSHA-102, work that was initiated in my laboratory in 2007, is a completely novel approach that allows for regulated expression of *MECP2* on a cell-by-cell basis. These results published today are highly encouraging and allow us to conceive additional novel approaches using miRARE in conditions with dose-sensitive genes."

"The complexities of developing an efficacious and well-tolerated gene therapy for the treatment of Rett syndrome are highlighted by phenotypic variability, mosaicism and the need to regulate *MECP2* such that it does not cause overexpression-related toxicity. Today's data give us confidence that we can achieve appropriate *MECP2* expression in all cells in a genotype-dependent manner, which we believe significantly de-risks the developmental program in its translation to humans," said Suyash Prasad, MBBS, M.Sc., MRCP, MRCPCH, FFPM, Chief Medical Officer and Head of Research and Development of Taysha. "Historically, unregulated gene replacement of *MECP2* resulted in overt adverse events, including death in wild type mice due to overexpression of the *MECP2* protein. With the built-in regulatory element, miRARE, TSHA-102 provided a statistically significant survival extension by 56% in 4- to 5-week-old knockout Rett mice. We see the potential for broadening the miRARE platform to other CNS diseases requiring regulated gene expression. These positive data support our intent to file an IND/CTA for TSHA-102 in the second half of this year, followed by initiation of a Phase 1/2 trial by year-end 2021. TSHA-102 has the potential to address a significant unmet need for an estimated 25,000 patient with Rett syndrome across the United States and in Europe."

The preclinical study was conducted by the UT Southwestern Medical Center (UT Southwestern) laboratory of Sarah Sinnett, Ph.D., and evaluated the safety and efficacy of regulated mini*MECP2* gene transfer, TSHA-102 (AAV9/mini*MECP2*-miRARE), via intrathecal (IT) administration in adolescent mice between four and five weeks of age. TSHA-102 was compared to unregulated full length *MECP2* (AAV9/*MECP2*) and unregulated mini*MECP2* (AAV9/mini*MECP2*).

TSHA-102 extended knockout survival by 56% via IT delivery. In contrast, the unregulated mini*MECP2* gene transfer failed to significantly extend knockout survival at either dose tested. Additionally, the unregulated full-length *MECP2* construct did not demonstrate a significant extension in survival and was associated with an unacceptable toxicity profile in wild type mice.

In addition to survival, behavioral side effects were explored. Mice were subjected to phenotypic scoring and a battery of tests including gait, hindlimb clasping, tremor and others to comprise an aggregate behavioral score. miRARE attenuated *MECP2*-mediated aggravation in wild type aggregate phenotype severity scores. Mice were scored on an aggregate severity scale using an established protocol. AAV9/*MECP2*- and AAV9/mini*MECP2*-treated wild type mice had a significantly higher mean (worse) aggregate behavioral severity score versus that observed for saline-treated mice ($p < 0.05$; at 6–30 and 7–27 weeks of age, respectively). TSHA-102-treated wild type mice had a significantly lower (better) mean aggregate severity score versus those of AAV9/*MECP2*- and AAV9/mini*MECP2*-treated mice at most timepoints from 11–19 and 9–20 weeks of age, respectively. No significant difference was observed between saline- and TSHA-102-treated wild type mice.

Of note, miRARE-mediated genotype-dependent gene regulation was demonstrated by analyzing tissue sections from wild type and knockout mice treated with AAV9 vectors given intrathecally. TSHA-102 demonstrated regulated *MECP2* expression in different regions of the brain. In the pons and

midbrain, miRARE inhibited mean *MECP2* gene expression in a genotype-dependent manner as indicated by significantly fewer myc(+) cells observed in wild type mice compared to knockout mice ($p<0.05$), thereby demonstrating that TSHA-102 achieved *MECP2* expression levels similar to normal physiological parameters.

“It has been a challenge finding an approach that can appropriately regulate *MECP2* expression in Rett syndrome but the preclinical data for TSHA-102 published today support the miRARE approach,” said Sarah Sinnett, Ph.D., Assistant Professor in the Department of Pediatrics at UT Southwestern. “It is clear that the disease is reversible, and I am encouraged that this novel strategy may enable us to make a difference in the management of this disease.”

The publication is available by clicking on the following link: https://academic.oup.com/brain/advance-article-abstract/doi/10.1093/brain/awab182/6265600.

About Taysha Gene Therapies

Taysha Gene Therapies (Nasdaq: TSHA) is on a mission to eradicate monogenic CNS disease. With a singular focus on developing curative medicines, we aim to rapidly translate our treatments from bench to bedside. We have combined our team’s proven experience in gene therapy drug development and commercialization with the world-class UT Southwestern Gene Therapy Program to build an extensive, AAV gene therapy pipeline focused on both rare and large-market indications. Together, we leverage our fully integrated platform—an engine for potential new cures—with a goal of dramatically improving patients’ lives. More information is available at www.tayshagtx.com.

Drs. Gray and Sinnett have intellectual property interest in Taysha and UTSW has a financial interest in the company.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as “anticipates,” “believes,” “expects,” “intends,” “projects,” and “future” or similar expressions are intended to identify forward-looking statements. Forward-looking statements include statements concerning the potential of our product candidates, including TSHA-102, to positively impact quality of life and alter the course of disease in the patients we seek to treat, our research, development and regulatory plans for our product candidates, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and whether, if approved, these product candidates will be successfully distributed and marketed, and the potential market opportunity for these product candidates. Forward-looking statements are based on management’s current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. Risks regarding our business are described in detail in our Securities and Exchange Commission (“SEC”) filings, including in our Annual Report on Form 10-K for the full-year ended December 31, 2020, which is available on the SEC’s website at www.sec.gov. Additional information will be made available in other filings that we make from time to time with the SEC. Such risks may be amplified by the impacts of the COVID-19 pandemic. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.

View source version on businesswire.com: https://www.businesswire.com/news/home/20210510005291/en/

Company Contact:
Kimberly Lee, D.O.
SVP, Corporate Communications and Investor Relations
Taysha Gene Therapies
klee@tayshagtx.com

Media Contact:
Carolyn Hawley
Canale Communications
carolyn.hawley@canalecomm.com

Source: Taysha Gene Therapies, Inc.