Taysha Gene Therapies Announces New Data on Multiple Preclinical Programs and Upcoming R&D Day

April 14, 2021

TSHA-113 significantly reduced tau mRNA and protein levels in mouse models of human tauopathies via cerebral spinal fluid (CSF) delivery supporting further preclinical development

TSHA-105 significantly reduced plasma citrate levels, normalized EEG brain activity, and reduced the number of seizures and seizure susceptibility in SLC13A5 knockout mice

TSHA-106 increased UBE3A expression through shRNA-mediated knockdown of UBE3A-ATS in in vitro cell lines across 26 distinct shRNA candidates for the treatment of Angelman disease

TSHA-112 generated significant reductions in GYS1 protein, abnormal glycogen accumulation and polyglucosan bodies in the APBD knockout mouse model

TSHA-111-LAFORIN and TSHA-111-MALIN achieved effective knockdown of GYS1 expression and insoluble glycogen and decreased Lafora body formation in laforin and malin mouse models

TSHA-119 caused a dose-dependent reduction of GM2 accumulation at 20 weeks in GM2A knockout mice

Positive proof-of-concept data for gene therapy candidates in SLC13A5 deficiency, APBD, Lafora disease and GM2 AB variant support advancement into clinical testing

Expect to submit IND/CTA for one of the following programs by the end of 2021: SLC13A5 deficiency, APBD, Lafora disease or GM2 AB variant

Taysha's virtual Research and Development Day in June 2021 will highlight progress across R&D pipeline

Dallas – April 14, 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 new data for multiple preclinical programs and a planned R&D Day, which will be held in June 2021.

"Collectively, these new preclinical data highlight Taysha's next wave of novel gene therapies that have the potential to impact meaningful patient populations. The promising data underscore our ability to rapidly and reproducibly investigate disease biology, design innovative gene therapies and efficiently advance the development of these drug candidates," said RA Session II, President, Founder and Chief Executive Officer of Taysha. "Among the compelling new data, for the first time, we have shown that TSHA-113, an AAV9 gene therapy that utilizes AAV-mediated gene silencing, reduced tau expression in mouse models of human tauopathies. The potential implications of these data are far reaching, and we intend to further evaluate TSHA-113 in additional preclinical studies. The totality of the preclinical data presented today support the fundamental elements of our scientific approach of coupling validated technology with novel targeted payload design while utilizing a proven HEK293 suspension manufacturing process. We believe our deep pipeline and innovative scientific engine hold tremendous potential, and we are poised to continue delivering meaningful value to patients with monogenic CNS diseases."

"Today's data demonstrate the breadth, depth and velocity of our development engine as a sustainable pivotal-stage gene therapy company. There are no approved disease modifying therapies for any of the programs in our portfolio and we are encouraged by the results of our gene therapy approach of vectorized RNA and gene replacement therapies across our portfolio," said Suyash Prasad, MBBS, M.SC., MRCP, MRCPCH, FFPM, Chief Medical Officer and Head of Research and Development of Taysha. "We are very excited to further develop TSHA-113 in tauopathies, including Alzheimer's disease, MAPT-associated frontotemporal dementia and progressive supranuclear palsy, based on the significant reduction in tau expression demonstrated in transgenic mouse models of human tauopathies. In addition, to date, we have advanced five programs into IND/CTA-enabling studies, including TSHA-105 in SLC13A5 deficiency, TSHA-111-LAFORIN in Lafora disease, TSHA-111-MALIN in Lafora disease, TSHA-112 in APBD and TSHA-119 in GM2 AB variant. We intend to file an IND/CTA for one of these five named programs by the end of 2021. By mid-year, we intend to select a development candidate for Angelman syndrome and obtain interim expression and safety data from confirmatory non-human primate studies by year-end. We remain on track to report Phase 1/2 biomarker data for TSHA-101 in GM2 gangliosidosis in the second half of this year and to provide a clinical and regulatory update for TSHA-120 in giant axonal neuropathy by year-end. Finally, in the second half of the year, we continue to expect dosing of the first patient with CLN1 disease in a Phase 1/2 trial for TSHA-118 under an already open IND, filing an IND/CTA for TSHA-102 in Rett syndrome and TSHA-104 in SURF1-associated Leigh syndrome, and filing an IND for TSHA-101 in GM2 gangliosidosis in the U.S. These anticipated clinical and regulatory milestones are expected to be followed by the initiation of Phase 1/2 clinical trials for each of these indications. We look forward to providing additional updates at our R&D Day in June."

TSHA-113 for Tauopathies

Taysha is developing tau-specific microRNA (miRNA) shuttles designed to target tau mRNA for all six isoforms found in the human brain and/or mouse brain. TSHA-113 is an AAV9 capsid that packages these miRNA shuttles and is delivered in the CSF for the treatment of tauopathies.

- In transgenic mouse models carrying human tau, TSHA-113 significantly reduced tau mRNA and protein levels, while demonstrating widespread expression in neurons and glia
- Together with previous *in vitro* findings, these data further validate selective reduction of tau mRNA and protein levels and warrant further preclinical development
- An estimated 6.2 million Americans and 7.8 million Europeans are living with Alzheimer's disease
- There are an estimated 13,000 patients in U.S. and Europe affected by MAPT-associated frontotemporal dementia, progressive supranuclear palsy and corticobasal degeneration, which represent a significant commercial opportunity

TSHA-105 for SLC13A5 deficiency

TSHA-105 is a recombinant self-complementary AAV9 vector that expresses the human SLC13A5 protein under the control of a ubiquitous promoter. The drug candidate is being developed for the treatment of SLC13A5 deficiency.

- In SLC13A5 knockout mice, treatment with TSHA-105 resulted in a significant, sustainable decrease of plasma citrate levels up to three months post-injection compared to age-matched, wildtype controls
- TSHA-105 normalized electroencephalogram (EEG) brain activity, reduced the number of seizures, and reduced seizure susceptibility compared to vehicle-treated controls
- The company has advanced TSHA-105 into IND/CTA-enabling studies
- There are an estimated 1,900 patients with SLC13A5 deficiency in the United States and in Europe

TSHA-106 for Angelman syndrome

TSHA-106 is an intrathecally delivered AAV9 viral vector designed for shRNA-mediated knockdown of UBE3A-ATS, the antisense transcript governing the expression of UBE3A through the paternal allele.

- *In vitro* testing in a neuroblast cell line demonstrated consistent knockdown of UBE3A-ATS and a subsequent increase in UBE3A expression across 26 distinct shRNA candidates
- Selection of development candidate expected by mid-year
- Interim expression and safety data from confirmatory non-human primate (NHP) studies expected by the end of 2021
- There are an estimated 55,000 patients with Angelman syndrome in the United States and Europe

TSHA-112 for Adult Polyglucosan Body Disease (APBD)

TSHA-112 is an intrathecally delivered AAV9 viral vector designed for miRNA-mediated knockdown of the *GYS1* gene to treat APBD.

- In preclinical studies, miRNA knockdown of GYS1 induced significant reductions in *GYS1* mRNA, GYS1 protein, abnormal glycogen accumulation, and polyglucosan bodies throughout the brain in an APBD knockout mouse model
- TSHA-112 decreased neuroinflammatory markers across three distinct mouse models
- The company has advanced TSHA-112 into IND/CTA-enabling studies
- There are an estimated 10,000 patients with APBD in the United States and in Europe

TSHA-111-LAFORIN for EPM2A and TSHA-111-MALIN for EPM2B for Lafora disease

TSHA-111-LAFORIN and TSA-111-MALIN are intrathecally delivered AAV9 viral vectors designed for miRNA-mediated knockdown of the *GYS1* gene to treat Lafora disease.

- In preclinical studies, TSHA-111-LAFORIN and TSHA-111-MALIN achieved effective knockdown of *GYS1* expression and insoluble glycogen in the Lafora disease laforin and malin mouse models, respectively
- Both product candidates decreased Lafora body formation within the brain in their respective mouse models
- The company has advanced TSHA-111-LAFORIN and TSHA-111-MALIN into IND/CTA-enabling studies
- There are an estimated 700 patients with Lafora disease in the United States and in Europe

TSHA-119 for GM2 AB variant

TSHA-119 is a self-complementary AAV9 vector designed to deliver a functional copy of the *GM2A* gene to treat GM2 AB variant.

- In preclinical studies, TSHA-119 caused a significant, dose-dependent reduction of GM2 accumulation at 20 weeks in mice that were dosed intrathecally at postnatal day 1 or at 6 weeks of age
- Long-term follow up studies, which include bi-monthly behavioral, as well as biochemical and histological analyses, are currently ongoing
- The company has advanced TSHA-119 into IND/CTA-enabling studies
- There are approximately 200 patients with GM2 AB variant in the United States and in Europe

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.

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 our preclinical product candidates, 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.

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