Taysha Gene Therapies Announces Initiation of Clinical Development of TSHA-102 in Rett Syndrome

Clinical Trial Application (CTA) approved by Health Canada in March 2022

TSHA-102, which utilizes novel miRARE platform to regulate transgene expression genotypically on a cell-by-cell basis, is the first-and-only gene therapy in clinical development for Rett syndrome

TSHA-102 improved survival, respiratory and motor function assessments in mouse models of Rett syndrome; biodistribution in non-human primates (NHP) supports miRARE mechanism of action; six-month NHP GLP toxicology data support the favorable safety and tolerability profile of TSHA-102

Preliminary Phase 1/2 clinical data for TSHA-102 expected by year-end 2022

DALLAS--(BUSINESS WIRE)--Mar. 29, 2022--

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 initiation of clinical development of TSHA-102 for the treatment of Rett syndrome under a recently approved Clinical Trial Application (CTA) by Health Canada. Sainte-Justine Mother and Child University Hospital Center in Montreal, Quebec, Canada has been selected as the initial clinical site under the direction of Dr. Elsa Rossignol, principal investigator. The company also announced positive preclinical data from IND/CTA-enabling studies including a pharmacology study in the Rett knockout mouse model (n=252) that assessed the efficacy of TSHA-102 and a Good Laboratory Practices (GLP) toxicology study of TSHA-102 in nonhuman primates (NHPs) (n=24) that explored biodistribution and mechanism of action, both of which supported authorization of the CTA.

“Initiation of clinical development is a significant milestone for the TSHA-102 program and Rett syndrome community,” said Suyash Prasad, MBBS, M.Sc., MRCP, MRCPCH, FFPM, Chief Medical Officer and Head of Research and Development of Taysha. “Treating Rett syndrome by gene replacement therapy requires an approach that can safely regulate transgene expression in a genotypic manner on a cell-by-cell basis without causing deleterious effects associated with overexpression. TSHA-102’s robust preclinical data package supports and validates the safe and controlled regulation of transgene expression using miRARE, a novel miRNA-responsive target sequence exclusively licensed to Taysha and developed by Drs. Sarah Sinnett and Steven Gray[1] of UT Southwestern Medical Center. Data from the 6-month non-human primate GLP toxicology study reinforced TSHA-102’s favorable safety profile across all dose levels tested including doses up to 4-fold above the presumed clinical starting dose. Data from the IND/CTA-enabling pharmacology study in mouse models of Rett syndrome demonstrated that miRARE regulated transgene expression improved survival, respiratory and motor function assessments across multiple dose levels. We continue to be highly encouraged by the therapeutic potential of TSHA-102.”

Dr. Prasad added, “There are no disease-modifying therapies to treat over 350,000 patients estimated to suffer from Rett syndrome worldwide [2]. We are excited to advance TSHA-102 as the first gene therapy in clinical development for the treatment of this devastating neurodevelopmental disorder and look forward to reporting preliminary Phase 1/2 clinical data by the end of 2022.”

Pharmacologic activity of TSHA-102 following intrathecal (IT) administration was assessed in the MECP2 knockout mouse model of Rett syndrome across three dose levels and three age groups (n=252). A one-time IT injection of TSHA-102 significantly increased survival at all dose levels, with the mid to high doses improving survival across all age groups compared to vehicle-treated controls. Treatment with TSHA-102 significantly improved body weight, motor function and respiratory assessments in MECP2 knockout mice. An additional study in neonatal mice is ongoing, and preliminary data suggest normalization of survival.

An IND/CTA-enabling 6-month GLP toxicology study (n=24) examined the biodistribution, toxicological effects and mechanism of action of TSHA-102 when intrathecally administered to NHPs across three dose levels. Biodistribution, as reflected by DNA copy number, was observed in multiple areas of the brain, sections of spinal cord and the dorsal root ganglion (DRG). Importantly, mRNA levels across multiple tissues were low, indicating miRARE regulation is minimizing transgene expression from the construct in the presence of endogenous MECP2 as expected, despite the high levels of DNA that were delivered. No toxicity from transgene overexpression was observed, confirmed by functional and histopathologic evaluations demonstrating no detrimental change in neurobehavioral assessments and no adverse tissue findings on necropsy.

These preclinical safety and efficacy data will be presented at the International Rett Syndrome Foundation (IRSF) Rett Syndrome Scientific Meeting taking place April 26-27, 2022 in Nashville, Tennessee.

[1]Dr. Steven Gray is Chief Scientific Advisor and a consultant for Taysha

[2]Source: Rett Syndrome Research Trust

About TSHA-102 and miRARE

TSHA-102 is a self-complementary intrathecally delivered AAV9 gene replacement therapy under development for the treatment of Rett syndrome. TSHA-102 utilizes the novel miRNA-Responsive Auto-Regulatory Element (miRARE) platform to regulate transgene expression genotypically on a

cell-by-cell basis. The miRARE technology is designed to prevent toxicity associated with transgene overexpression and can be potentially utilized across other indications. Health Canada has authorized the CTA for TSHA-102 and Sainte-Justine Mother and Child University Hospital has been selected as the initial clinical site under the direction of Dr. Elsa Rossignol, principal investigator. Preliminary Phase 1/2 clinical data for TSHA-102 is expected by the end of 2022. TSHA-102 has received rare pediatric disease designation and orphan drug designation from the U.S. Food and Drug Administration and orphan drug designation from the European Commission.

About Rett Syndrome

Rett syndrome is a severe genetic neurodevelopmental disorder caused by a mutation in the X-linked MECP2 gene essential for neuronal and synaptic function in the brain. Primarily occurring in females, Rett syndrome is one of the most common genetic causes of severe intellectual disability worldwide, with a prevalence of over 350,000 patients worldwide[2]. Patients have normal early development, with symptom onset typically beginning between 6 to 18 months of age. Rett syndrome is characterized by rapid developmental regression that leads to intellectual disabilities, loss of speech, loss of purposeful use of hands, loss of mobility, seizures, cardiac impairments and breathing issues. Currently, there are no approved therapies that treat the underlying cause of this progressive disease.

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 goa 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 the TSHA-102 in Rett syndrome, 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, and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, both of which are 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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Company Contact:
Kimberly Lee, D.O.
Chief Corporate Affairs Officer
Taysha Gene Therapies
klee@tayshagtx.com

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

Source: Taysha Gene Therapies, Inc.