Neurogene Announces FDA Clearance of IND for NGN-401 Gene Therapy for Children with Rett Syndrome

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Planned NGN-401 Phase 1/2 clinical trial to dose female pediatric patients with Rett syndrome in 2023

In a comprehensive preclinical program, NGN-401 demonstrated robust therapeutic and safety benefits, delivering MECP2 to key brain regions affected by Rett syndrome

NGN-401 utilizes Neurogene's proprietary EXACT technology to regulate transgene expression, and is the first and only gene therapy for Rett syndrome transferring the full-length MECP2 gene

NGN-401, manufactured at Neurogene's GMP facility, is Neurogene's second investigational gene therapy product candidate to enter the clinic in the United States

NEW YORK, January 23, 2023 – Neurogene Inc., a clinical-stage company founded to bring life-changing genetic medicines to patients and families affected by rare neurological diseases, today announced that the U.S. Food and Drug Administration (FDA) has cleared the Company's Investigational New Drug (IND) application for NGN-401 for the treatment of Rett syndrome.

NGN-401 is the first investigational adeno-associated virus (AAV) gene therapy candidate to be administered to pediatric patients using Neurogene's proprietary Expression Attenuation via Construct Tuning (EXACT) gene regulation technology. EXACT, developed in collaboration with the University of Edinburgh, is a self-contained, transgene regulation technology that can be tuned to deliver a desired level of transgene expression within a narrow range, and is compatible with viral and non-viral delivery platforms. Embedding EXACT technology into NGN-401 is an important advancement in gene therapy for Rett syndrome, specifically because the disorder requires a treatment approach that safely regulates *MECP2* transgene expression without causing toxic effects associated with overexpression.

Intracerebroventricular (ICV) delivery of NGN-401 was evaluated in multiple preclinical models, including the male MECP2 knock out mouse model for efficacy, the female MECP2 mouse model for tolerability, and non-human primates (NHPs) for toxicity. Notably, the efficacy profile for NGN-401 was robust, demonstrating a significant survival benefit with concomitant improvements in Rett syndrome-like phenotypes compared to untreated control animals. Importantly, expression data for NGN-401 demonstrated well-controlled MeCP2 protein levels in key brain regions affected by Rett syndrome, while conventional gene therapy, without EXACT regulation, generated more variable and undesirable higher MeCP2 levels. While comparable doses of NGN-401 in female mice and in NHPs were safe and well-tolerated, in stark contrast, conventional *MECP2* gene therapy without EXACT regulation showed severe toxicity in mice and early signs of toxicity in NHPs.

"Rett syndrome is a particularly challenging disorder for gene therapy because of the requirement to deliver therapeutic levels of *MECP2*, without also triggering significant side effects associated with too much gene expression," said Rachel McMinn, Ph.D., CEO and Founder of Neurogene. "We believe the preclinical profile for NGN-401 is highly compelling, with the strongest results generated to date across multiple animal models. FDA clearance of NGN-401 represents a significant milestone for Neurogene and the Rett syndrome community and underscores our commitment to turn devastating neurological diseases into treatable conditions, and to improve the lives of patients and families impacted by these rare diseases."

"Rett syndrome is a debilitating disease with a devastating impact on children and their families, with no disease-modifying treatments available," said Dr. Bernhard Suter, Assistant Professor of Pediatrics and Neurology at Baylor College of Medicine and neurologist at Texas Children's Hospital. "The upcoming clinical study of NGN-401, which has a mechanism of action aimed at addressing the root cause of disease, offers hope for improving the lives of those suffering from Rett syndrome."

Neurogene recognizes the U.S. Rett syndrome patient advocacy organizations, the Rett Syndrome Research Trust (RSRT) for funding foundational Rett syndrome research at the University of Edinburgh, and the International Rett Syndrome Foundation (IRSF). We appreciate both the RSRT and the Clinical Trial Committee of the IRSF for their extensive collaboration and significant input into the clinical trial design, as well as the large number of caregivers and expert clinicians who provided their unique insights into the key disease manifestations of Rett syndrome. Feedback from all stakeholders, including the FDA, is incorporated into the Phase 1/2 clinical trial design.

IND clearance enables Neurogene to initiate a Phase 1/2 trial to assess the safety, tolerability and efficacy of NGN-401 in female pediatric patients with Rett syndrome. The open-label, single-arm, multi-center clinical trial will evaluate a single dose of NGN-401 delivered using a one-time ICV procedure. More details about the trial design will become available on www.clinicaltrials.gov.

About NGN-401
NGN-401 is an adeno-associated virus (AAV) gene therapy investigational product that is the first to deliver the full-length human *MECP2* gene, under the control of Neurogene's EXACT self-contained gene regulation technology. EXACT enables therapeutic levels of the protein MeCP2 while avoiding overexpression related toxicities. NGN-401 has received FDA clearance to be dosed in a one-time administration using the ICV procedure, which Neurogene has shown achieves broad vector distribution to key regions of the brain affected in Rett syndrome. NGN-401 has undergone extensive preclinical study and has demonstrated a robust efficacy profile, coupled with lack of MeCP2 protein related toxicities, even at high doses not intended for human use. NGN-401 is manufactured at Neurogene's GMP manufacturing facility, located in Houston, TX.

About EXACT
Expression Attenuation via Construct Tuning (EXACT) is Neurogene's proprietary gene regulation platform technology, developed in collaboration with the University of Edinburgh. EXACT was created to address key limitations of conventional gene therapy, in which cells receiving multiple copies of an AAV therapeutic are "overdosed" with transgene, resulting in transgene related toxicities. EXACT is a self contained gene regulation platform technology that can be tuned to deliver a desired level of transgene expression within a narrow range, thus avoiding transgene toxicities. EXACT is compatible with viral and non-viral delivery platforms, and as delivery methods improve, it may prove to be an important safety tool in gene therapy

designs across disease areas.

About Rett Syndrome
Rett syndrome is an X-linked, progressive, neurodevelopmental disorder. Rett syndrome has an estimated incidence of 1 in 10,000 live female births, making it one of the most common genetic causes of developmental and intellectual impairment in females. The incidence in males is currently unknown.

Rett syndrome is caused by mutations in the *MECP2* gene that lead to deficiency of the methyl cytosine binding protein 2 (MeCP2), an important protein responsible for normal function in the brain and other parts of the nervous system. Females with Rett syndrome typically have normal development up until 6-18 months of age. However, females then experience rapid regression of previously acquired milestones including speech, gross and fine motor skills, and develop stereotypical, repetitive hand movements that prevent them from purposeful hand movement or function. Over time females may develop muscle contractures, rigidity, and debilitating scoliosis, along with periods of recurrent seizures, burdensome gastrointestinal abnormalities, breathing abnormalities and cognitive decline.

There are no approved disease-modifying therapies for Rett syndrome. Current treatments for Rett syndrome include symptom management and supportive care.

About Neurogene Inc.
The mission of Neurogene is to turn devastating neurological diseases into treatable conditions to improve the lives of patients and families impacted by these rare diseases. Neurogene is developing novel approaches and treatments to address the limitations of conventional gene therapy in CNS disorders. This includes selecting a delivery approach to maximize distribution to target tissues and by designing products to maximize potency and purity for an optimized efficacy and safety profile. The company's proprietary EXACT gene regulation platform technology allows for the delivery of therapeutic levels while limiting transgene toxicity associated with conventional gene therapy. For more information, visit www.neurogene.com.

Media Contact
Gwen Fisher
gwen@fishertrentcommunications.com