Newborn Screening Study for AADC Deficiency Published in Molecular Genetics and Metabolism

Study highlights frequency of AADC deficiency

Cambridge, MA, June 2, 2016, 7:30 am EST - Agilis Biotherapeutics (Agilis), a biotechnology company advancing innovative gene therapies for rare genetic diseases that affect the central nervous system (CNS), announced today the publication of the results of a newborn screening study for Aromatic L-Amino Acid Decarboxylase (AADC) deficiency. The study, "3-O-methyldopa levels in newborns: Result of newborn screening for aromatic L-amino-acid decarboxylase deficiency," published in *Molecular Genetics and Metabolism* (online May 2016) is authored by Agilis' collaborator, Dr. Paul Hwu, and colleagues at National Taiwan University (NTU) Hospital. Using the simple dried blood spot test, Dr. Hwu and colleagues screened 127,987 newborns in Taiwan from September 2013 to December 2015, identifying four newborns with elevated 3-O-methyldopa (3-OMD) concentration (subsequently confirmed as AADC deficiency by genetic sequencing) for an estimated incidence of AADC deficiency of 1:32,000 (95% confidence interval: 1:12,443-1:82,279). The false-positive and false-negative rates were zero.

"This work at National Taiwan University is an impressive demonstration of newborn screening methods for rare genetic and neurotransmitter disorders, and an important step forward for AADC deficiency," said Keith Hyland, PhD, a noted expert in AADC deficiency and Executive Vice President at MNG Laboratories. "Availability of robust, yet simple, tests for the disease may

help improve diagnostic accuracy and identify patients who can benefit from medical intervention."

AADC deficiency is a rare CNS disorder arising from mutations in the DDC gene that reduce the levels of the enzyme AADC. Reductions in AADC lead to deficits in multiple neurotransmitters, including dopamine. Dopamine is ordinarily formed from its precursor called L-dopa. When AADC activity is reduced, levels of the L-dopa precursor rise, and a by-product called 3-OMD is formed. The diagnosis of AADC deficiency is typically established by measuring the levels of neurotransmitter metabolites in cerebrospinal fluid obtained via lumbar puncture. Clinically, AADC deficiency is associated with severe developmental delay and inability to develop motor strength and control (global muscular hypotonia/dystonia). In its profound forms, these deficits result in breathing, feeding, and swallowing problems, frequent hospitalizations, and premature death within the first decade of life.

"AADC deficiency is a rare disorder, with an often catastrophic clinical course," said Dr. Paul Hwu, MD, Professor of Pediatrics at NTU and senior author on the publication. "This study is the first to empirically document the incidence of AADC deficiency in a prospective screening study and identifies a frequency in this patient population that is higher than previously estimated. Given the incidence of AADC deficiency and the confusion of symptoms with more common disorders such as cerebral palsy, this study marks a milestone in characterizing the incidence of this disorder and suggests that misdiagnosis may be more common than previously thought. It highlights the importance of awareness of AADC deficiency in assessing patients with neurological disorders characterized by hypotonia and dystonia."

Newborn screening for AADC deficiency has not been implemented in part because of the lack of availability and standardization of non-invasive testing methods, suited for screening. Recently, a simple, low cost, reliable test using a dried blood spot has been developed to test for 3-OMD levels. Because the clinical presentation of AADC deficiency shares similarities with more common disorders such as cerebral palsy and seizure disorders, AADC deficiency may be

misdiagnosed, and a straightforward screening test would be an important complement to facilitate diagnosis.

“Early ascertainment is key for optimal clinical management and care, and will be of paramount importance, with the emergence of gene therapy for AADC deficiency,” said Christopher Silber, MD, Agilis Chief Medical Officer. “The rigorous demonstration of the incidence of this disorder enhances our commitment to developing our novel gene therapy treatment for these patients who often have few, if any, treatment options. We continue to believe the AADC gene therapy program is one of the most advanced CNS gene therapy programs in the world, and we are on course to take the next steps in clinical development later this year.”

In January, Agilis announced that it had entered into an exclusive worldwide agreement with NTU for the treatment of AADC deficiency using gene therapy developed by Dr. Hwu and NTU Hospital. The AADC gene therapy program has treated 18 patients in two prospective clinical cohorts. Following a single administration of the gene therapy, treated subjects have exhibited substantial, durable gains in motor and cognitive function over multiple years, shown de novo production of dopamine as visualized by F-DOPA PET imaging, and realized improvements in metabolic biomarkers. In contrast, natural history cases routinely fail to achieve developmental milestones and show continued clinical deterioration as the disease course progresses. In collaboration with NTU, Agilis is now preparing for a Phase IIb clinical study. In preparing the program for clinical trials, The University of Florida Powell Gene Therapy Center was instrumental in the development of the initial product manufacturing and toxicology work.

About AADC Deficiency

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare genetic condition resulting from deficits in the enzyme, AADC, which is responsible for the final step in the synthesis of the neurotransmitters dopamine (a precursor of norepinephrine and epinephrine) and serotonin (a precursor of melatonin). AADC deficiency arises from mutations in the dopa decarboxylase

(DDC) gene. In its profound forms, AADC deficiency results in severe developmental failure, global muscular hypotonia and dystonia, severe, long-lasting episodes known as oculo-gyric crises, frequent hospitalizations (including prolonged stays in intensive care), and the need for life-long care. Symptoms and severity vary depending on the type of underlying genetic mutation which abrogates AADC enzyme function. Severe forms of the disease can arise from specific DNA mutations. Patients with severe forms usually die before the age of seven years due to extreme motor dysfunction, autonomic abnormalities, and secondary complications such as choking, hypoxia, and pneumonia. No treatment options other than palliative care currently exist for patients with severe AADC deficiency.

About Agilis Biotherapeutics

Agilis is advancing innovative gene therapies designed to provide long-term efficacy for patients with debilitating, often fatal, rare genetic diseases that affect the central nervous system. Our therapies are engineered to impart sustainable clinical benefits, and potentially a functional cure, by inducing persistent expression of a therapeutic gene. The Company's technology is aimed at the precise targeting and restoration of a lost gene function, while avoiding unintended off-target effects. Our integrated strategy increases the efficiency of developing DNA therapeutics into safe, targeted gene therapies that achieve long-term efficacy and enable patients to remain asymptomatic without continuous invasive treatment. Agilis' rare disease programs are focused on gene therapy for AADC deficiency, Friedreich's ataxia, Angelman syndrome, and Fragile X syndrome, rare genetic diseases that include severe neurological deficits and result in physically debilitating conditions.

We invite you to visit our website at www.agilisbio.com

Safe Harbor Statement

Some of the statements made in this press release are forward-looking statements. These forward-looking statements are based upon our current expectations and projections about

future events and generally relate to our plans, objectives and expectations for the development of our business. Although management believes that the plans and objectives reflected in or suggested by these forward-looking statements are reasonable, all forward-looking statements involve risks and uncertainties and actual future results may be materially different from the plans, objectives and expectations expressed in this press release.

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