Agilis Biotherapeutics Updates on Progress in CNS Gene Therapy Programs

Planned Dosing in Phase IIb Study of AADC Deficiency Gene Therapy Completed; BLA Preparation Underway Following FDA Meeting

Friedreich Ataxia and Angelman Syndrome INDs on Track for 2018 and 2019, Respectively

Novel Forms of Reelin Protein in Proof-of-Concept Studies to Select First Target Indications

Cambridge, MA, October 3, 2017 -- Agilis Biotherapeutics, Inc. (Agilis), a biotechnology company advancing innovative DNA therapeutics for rare genetic diseases that affect the central nervous system (CNS), announced today that dosing of the last of six planned patients has been completed in the ongoing Phase IIb clinical study for the Company’s gene therapy for the treatment of Aromatic L-amino acid decarboxylase (AADC) deficiency, the third prospective study conducted on the AADC gene therapy, termed AGIL-AADC. The cohort of patients in the Phase IIb study brings the total number of patients who have received AGIL-AADC to 24, likely representing the largest cohort of patients in any CNS gene therapy program. AADC deficiency is a rare disease of young children with a devastating clinical course requiring substantial life-long care for severe neurologic impairment arising from mutation in the DDC gene encoding the AADC enzyme. AADC is the enzyme that produces dopamine and serotonin in the brain. Symptoms of AADC deficiency include the complete absence of motor milestone development, seizure-like events (termed oculogyric crisis) and severe hypotonia often described as “floppiness”. The disease can be confused with other, more common disorders such as cerebral palsy, making diagnosis difficult and often leading to a protracted diagnostic odyssey in correctly identifying the disease.

Based on multi-year safety and efficacy data from initial clinical studies with AGIL-AADC and feedback at a recent End-of-Phase-II meeting with the U.S. Food and Drug Administration (FDA), Agilis has started preparation of a Biologics License Application (BLA) for AGIL-AADC, targeted for submission by the end of 2018.

The Company may extend the Phase IIb study to permit the treatment of additional patients in need of therapeutic intervention while it undertakes activities in support of the approval of AGIL-AADC in multiple countries around the world.
**Gene Therapy Effect on Dopamine Production and Motor Function in Children with Severe AADC Deficiency**

Combined results to date from the first two open-label clinical studies encompassed 18 patients with severe AADC deficiency ranging from 21 months to 8.5 years of age, each of whom received a single administration of AGIL-AADC at a dose of 1.8x10e11 vg total delivered to the putamen. At baseline, patients had no functional movement and failed to achieve any motor milestones, including head control, sitting or standing capabilities, consistent with the published natural history of severe AADC deficiency (Wassenberg et al. 2017). Compared to baseline at one-year and at five-years after AGIL-AADC administration, patients had objective evidence of de novo dopamine production as visualized by F-DOPA PET imaging of the brain, consistent with successful and stable DDC gene transduction over time. After administration of AGIL-AADC, the combined group of patients showed significant change from baseline capabilities at one-year post-treatment in functional motor skills assessed with the Peabody Developmental Motor Scale, Second Edition (PDMS-2) total score (p<0.00001) as well as locomotion, grasping, visual-motor integration and stationary subscales (all p<0.00001). Similar changes from baseline at one-year post-treatment were also observed for the combined group of patients on the Alberta Infant Motor Scale (AIMS) total score (p<0.0001) and prone, supine and sit subscales (all p<0.0001) and the stand subscale (p=0.003). Compared to published natural history data (Wassenberg et al. 2017), patients showed statistically significant improvements at both two- and five-years post-treatment in achievement of motor milestones of full head control (p<0.0001 at two and five years), sitting unassisted (p=0.0004 at two years; p<0.0001 at five years) and standing with support (p=0.005 at five years), reinforcing the clinical benefit and sustainability of functional motor improvements. The PDMS-2 and AIMS are validated scales used to assess motor skills in young children.

Kirsten Gruis, M.D., Agilis Chief Medical Officer, said, “The emerging clinical data indicating sustained motor function improvements following a single administration of AGIL-AADC gene therapy are encouraging, with patients achieving and maintaining motor milestones that would not otherwise be seen in children with severe AADC deficiency. Over the period of observation, important functional gains have been observed to date in the context of a good safety and tolerability profile. These data support the premise that gene therapy may be able to provide durable benefits to patients with debilitating disorders affecting the central nervous system.”
In preparation for the BLA submission, approval and ultimately commercial launch, the Company has selected the commercial manufacturer for AGIL-AADC and is commencing initial market preparation activities. Efforts are underway for multi-national registration, including initiation of the process for the submission of a Marketing Authorization Application (MAA) in Europe and pilot efforts in Asia, including the formation of a recently-announced joint venture with the Gene Therapy Research Institution (GTRI) in Japan.

AGIL-AADC has Orphan Drug Designation and Rare Pediatric Disease (RPD) designation in the U.S., and Orphan Medicinal Product status in Europe. The U.S. Orphan designation allows Agilis to leverage the FDA’s Priority Review pathway, hastening patient access to AGIL-AADC by shortening the review of the marketing application by as much as four months. The complementary RPD designation gives Agilis the ability to qualify for a Priority Review Voucher (PRV) upon approval of AGIL-AADC. PRV’s can be redeemed or transferred to a third party to receive Priority Review on a subsequent marketing application for a different product. This voucher will be requested at the time of the marketing application and awarded upon approval. AGIL-AADC has been developed in collaboration with National Taiwan University and the U.S. National Institutes of Health’s National Center for Advancing Translational Sciences (NCATS) through a Cooperative Research and Development Agreement (CRADA). NCATS recently provided an update on the progress of and outlook for the AADC gene therapy: [https://ncats.nih.gov/news/releases/2017/trnd-agilis](https://ncats.nih.gov/news/releases/2017/trnd-agilis). Additionally, Christopher P. Austin, MD, Director of NCATS, also recently delivered a presentation on the AADC gene therapy program as part of a NCATS Advisory Council meeting, which is archived and can be viewed at [www.agilisbio.com/news](http://www.agilisbio.com/news).

“We are pleased with the rapid progress and BLA positioning for our AADC program. The outcome of the recent FDA meeting highlights the potential benefits observed in patients treated thus far,” said Mark Pykett, President and CEO of Agilis. “We look forward to the preparation of the BLA and to marketing authorization activities in other countries as we strive to bring this potential treatment to patients with AADC deficiency around the world.”

**Pipeline Progress**

Agilis continues to make significant strides in its other pipeline programs.
Friedreich Ataxia

The Company’s program in Friedreich ataxia (FA), AGIL-FA, an AAV-based vector for delivery of the human FXN gene intended to address the CNS manifestations of FA, is advancing rapidly through nonclinical, manufacturing and regulatory activities toward human clinical study. FA is a debilitating monogenic disorder arising from mutation in the FXN gene encoding the mitochondrial protein frataxin, resulting in severe neurological symptoms and impairment of quality of life and often leading to cardiomyopathy. Neurologically, patients experience progressive ataxia with severely impaired coordination of voluntary muscle movement with eventual loss of ambulation and independent functioning as well as slurred speech, scoliosis, vision loss and sensorineural hearing impairment. Agilis has generated a proprietary library of optimized FXN gene constructs through engineering of promotor and gene regulatory elements tied to the wild-type FXN gene in collaboration with Intrexon Corporation (NASDAQ: XON), resulting in novel compositions of matter and intellectual property. In vitro characterization, including analyses in inducible pluripotent stem cell systems, has verified the critical functional parameters of the optimized FXN gene and frataxin protein, leading to selection of the AGIL-FA lead construct. Analyses of routes of CNS administration and biodistribution of the optimized lead construct using the selected AAV vector have been completed in five in vivo IND-enabling non-clinical studies, demonstrating reproducible targeting of the FXN gene to, and expression of the frataxin protein in, target CNS cells that data suggest are integral to CNS manifestations in FA. The Company has completed a pre-IND meeting with the FDA and is on track to open an IND in 2018.

Angelman Syndrome

Agilis’ gene therapy program for Angelman syndrome (AS) is completing final analyses for lead selection of the AAV-based gene therapy. AS is a severe neurological disorder arising from mutation of a single gene, UBE3A, which encodes the ubiquitin ligase E6-AP, leading to a range of cognitive symptoms, including developmental delay, deficits in learning and memory, absent speech, seizures and a characteristic ataxia. The Company has analyzed a series of AAV vector-UBE3A gene assemblies, including a potentially potent novel secreted form of the UBE3A protein product, the ubiquitin ligase E6-AP. Proof-of-concept with the wild type and secreted forms of the protein product has been demonstrated in a gold-standard AS model. In vivo studies have been completed evaluating the effects of route of administration and dosing of candidate AAV vectors on CNS biodistribution and targeting of key brain structures believed to be central to the pathogenesis and symptoms of AS. Lead selection is
anticipated by the end of 2017 in support of a pre-IND meeting with the US FDA and scientific advice in Europe, and IND-enabling studies in 2018, and clinical study in 2019.

Reelin

The Company’s program in Reelin therapy has taken critical steps toward developing therapeutics in a range of disorders characterized by cognitive impairment, including potential uses in neurodegenerative, neurotraumatic and neuropsychiatric indications. Reelin is a protein thought to impart multiple effects to neurons via interactions with ApoER2 and VLDLR receptors, potential steric interference of beta-amyloid, alterations in tau protein phosphorylation, and modulation of APMA and NMDA neuronal signaling pathways. Initial proof-of-concept of Reelin effects has been obtained in multiple disease models. Novel fragments of the Reelin gene and corresponding protein conveying Reelin function have been identified, comprising new composition of matter patent applications. In vivo studies are underway evaluating target indications and potential AAV vectors for CNS delivery of full-length and truncated forms of Reelin. If successfully developed, Reelin treatments may be targeted to a diverse range of potential indications representing significant medical opportunities in which effective approved treatment options are limited, such as stroke, schizophrenia, and Fragile-X syndrome.

Progress across the Company’s pipeline has been enabled by the $23M Series B financing completed earlier this year, led by Sands Capital Ventures with strong insider participation.

About Agilis Biotherapeutics, Inc.

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. Agilis’ gene therapies are engineered to impart sustainable clinical benefits by inducing persistent expression of a therapeutic gene through precise targeting and restoration of lost gene function to achieve long-term efficacy. Agilis’ rare disease programs are focused on gene therapy for AADC deficiency, Friedreich’s ataxia, and Angelman syndrome, all rare genetic diseases that include neurological deficits and result in physically debilitating conditions.

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

Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare monogenetic condition caused by mutations in the DDC gene resulting in lack of functioning AADC enzyme responsible for the final step in the synthesis of key neurotransmitters dopamine (a precursor of norepinephrine and epinephrine) and serotonin (a precursor of melatonin). AADC deficiency affects infants and young children and results in developmental failure, global muscular hypotonia, severe, seizure-like episodes known as oculogyric crises, autonomic abnormalities, and the need for life-long care. Given this neurologically devastating illness, patients with severe AADC deficiency have a high risk for death during childhood. Treatment options for patients with AADC deficiency are limited and there are currently no approved therapies.

About Friedreich Ataxia

Friedreich ataxia (FA) is an inherited, monogenetic ataxia syndrome caused by a genetic defect in the FXN gene that leads to reduced production of frataxin, a key mitochondrial protein for ATP production. FA is the most common hereditary ataxia, with an estimated 5,000 to 10,000 patients in the U.S. (i.e., one in every 50,000 people). Onset of FA is typically in childhood with symptoms of progressive ataxia with impaired coordination of volitional muscle movements, slurred speech, and loss of ambulation after 10-15 years resulting in severe disability. Patients also develop scoliosis (which often requires surgical intervention), diabetes mellitus, hearing and vision impairments, and a serious cardiomyopathy that results in premature death in early adulthood. Current FA therapies are primarily focused on symptomatic relief, and there are no FDA-approved drugs to treat the cause of FA.

About Angelman Syndrome

Angelman syndrome (AS) is a rare monogenetic disorder caused by the deletion/mutation of the UBE3A gene encoding the ubiquitin ligase E6-AP, a protein which plays a critical role in the function of the central nervous system. AS affects young children with symptoms of delayed motor development, severe learning disability, absent speech, seizures and ataxia, resulting in chronic disability and the need for lifelong care. According to The Foundation for Angelman Syndrome Therapeutics, the disorder strikes an estimated 1 in 15,000 live births.

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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