Denali Therapeutics Announces FDA Has Selected DNL126 (ETV:SGSH) for MPS IIIA (Sanfilippo Syndrome Type A) for START Pilot Program Intended to Accelerate Development of Rare Disease Therapies

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- START is a pilot program newly launched jointly by the FDA CDER and CBER divisions to further accelerate the development of novel drug and biological products for rare diseases
- DNL126 was selected as one of three CDER-regulated products based on eligibility criteria including the potential for clinical benefit for a rare neurodegenerative disease and the drug sponsor's ability to advance development towards a marketing application
- Participation in START is expected to facilitate and accelerate development of DNL126 through more rapid and ad hoc communication with FDA review staff

SOUTH SAN FRANCISCO, Calif., June 03, 2024 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (Nasdaq: DNLI), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for the treatment of neurodegenerative and lysosomal storage diseases, today announced that the U.S. Food and Drug Administration (FDA) has selected DNL126 for participation in the Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program. DNL126 is an investigational enzyme replacement therapy designed to cross the BBB for the potential treatment of MPS IIIA (Sanfilippo syndrome type A).

The FDA announced the START Pilot Program on September 29, 2023, with the stated purpose to further accelerate the pace of development of novel drug and biological products that are intended to address an unmet medical need as a treatment for a rare disease. Selected participants of the START Pilot Program are provided opportunities to obtain frequent advice and engage in more rapid ad hoc communication with FDA review staff to address product-specific development issues. The START pilot and metrics are milestone driven and agreed upon by the FDA and sponsor. Initial selection for START planned to include up to six eligible programs (three each) from the FDA's Center for Biologics Evaluation and Research's (CBER) Office of Therapeutic Products and Center for Drug Evaluation and Research's (CDER) Office of New Drugs.[1]

"We are thrilled to be selected by the FDA for participation in START and see this as another important opportunity to work together to solve challenges unique to rare disease drug development," said Carole Ho, M.D., Chief Medical Officer of Denali. "It is an exciting time to be part of the collective effort of making new treatments available to individuals and families living with rare diseases. We look forward to continued collaboration with CDER to determine the most efficient development path for DNL126 in MPS IIIA, a devastating and progressive disease for which treatments are urgently needed."

Denali is conducting a Phase 1/2 study of DNL126 for children with MPS IIIA, which has generated high interest from the MPS IIIA community for whom there are no approved treatment options. As a selected START participant, Denali anticipates the increased level of engagement will facilitate alignment on the most efficient development path to ultimately support a marketing application for DNL126 in MPS IIIA.

Denali is also developing tividenofusp alfa (DNL310) as a potential treatment for people living with MPS II (Hunter syndrome) and expects to complete enrollment of the Phase 2/3 COMPASS study this year. Given the advanced development stage of the program, Denali did not apply to START for tividenofusp alfa. The FDA granted Fast Track designation to tividenofusp alfa, which also facilitates increased communication and engagement with the FDA specific to this program.

About MPS IIIA (Sanfilippo syndrome Type A)
MPS III, also called Sanfilippo syndrome, is a rare, genetic lysosomal storage disease that causes neurodegeneration. There are four main types of MPS III, depending on the enzyme affected. Type A is caused by genetic defects that result in reduction in the activity of N-sulfoglucosamine sulfohydrolase (SGSH), an enzyme responsible for degrading heparan sulfate in the lysosome. There are no approved treatments for MPS IIIA. A natural history study of biomarkers and adaptive behavior in MPS IIIA is ongoing and more information can be found here.

About DNL126 (ETV:SGSH)
DNL126 (ETV:SGSH) is an investigational, intravenously administered, Enzyme Transport Vehicle (ETV)-enabled N-sulfoglucosamine sulfohydrolase (SGSH) replacement therapy designed to cross the BBB via receptor-mediated transcytosis into the brain and to enable broad delivery of SGSH into cells and tissues throughout the body with the goal of addressing the behavioral, cognitive, and physical manifestations of MPS IIIA.

About the Phase 1/2 study of DNL126

Denali is conducting a multicenter, open-label, Phase 1/2 study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory clinical efficacy of DNL126 in participants with MPS IIIA. The core study period is approximately 6 months and is followed by an open-label extension for approximately 18 months. More information about the Phase 1/2 study can be found here.

About tividenofusp alfa (DNL310)
Tividenofusp alfa (DNL310) is a fusion protein composed of iduronate 2-sulfatase (IDS) fused to Denali's proprietary Enzyme Transport Vehicle (ETV), which is engineered to cross the BBB via receptor-mediated transcytosis into the brain and to enable broad delivery of IDS into cells and tissues throughout the body with the goal of addressing the behavioral, cognitive, and physical manifestations of MPS II. In March 2021, the U.S. Food and Drug Administration granted Fast Track designation to DNL310 for the treatment of patients with MPS II. In May 2022, the European Medicines Agency granted DNL310 Priority Medicines designation. DNL310 is an investigational product candidate and has not been approved by any Health Authority.

About the Phase 2/3 COMPASS study of tividenofusp alfa
Based on supportive clinical and preclinical data to date, Denali is enrolling the Phase 2/3 COMPASS study in North America, South America, and Europe. The Phase 2/3 COMPASS study is expected to enroll 54 participants with MPS II with and without neuronopathic disease. The participants are randomized 2:1 to receive either tividenofusp alfa (DNL310) or idursulfase, respectively. Cohort A includes children ages 2 to 6 with neuronopathic disease; cohort B includes children ages 6 to 17 without neuronopathic disease. Upon completion of the ongoing Phase 1/2 study, and together with data from the global COMPASS study, this combined data package is intended to support registration. More information about the COMPASS study can be found here.

About Denali's Transport Vehicle Platform
The blood-brain barrier is essential in maintaining the brain's microenvironment and protecting it from harmful substances and pathogens circulating in the bloodstream. Historically, the blood-brain barrier has posed significant challenges to drug development for central nervous system diseases by preventing most drugs from reaching the brain in therapeutically relevant concentrations. Denali's Transport Vehicle platform is a proprietary technology designed to effectively deliver large therapeutic molecules such as antibodies, enzymes, proteins, and oligonucleotides across the blood-brain barrier after intravenous administration. The Transport Vehicle technology is based on engineered Fc domains that bind to specific natural transport receptors, such as transferrin receptors, which are expressed at the blood-brain barrier and deliver the Transport Vehicle and its therapeutic cargo to the brain through receptor-mediated transcytosis. In animal models, antibodies and enzymes engineered with the Transport Vehicle technology demonstrate more than 10- to 30-fold greater brain exposure than similar antibodies and enzymes without this technology. Improved exposure and broad distribution in the brain may increase therapeutic efficacy by enabling widespread achievement of therapeutically relevant concentrations of product candidates.

About Denali Therapeutics

Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for the treatment of neurodegenerative and lysosomal storage diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the BBB and guiding development through biomarkers that demonstrate target and pathway engagement. Denali is based in South San Francisco. For additional information, please visit www.denalitherapeutics.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements expressed or implied in this press release include, but are not limited to, statements regarding Denali's plans, timelines, and expectations related to DNL126, including the ongoing Phase 1/2 study; expectations with respect to the START program, including interactions with the FDA, overall development plans, and pathway for approval; plans, timelines, and expectations related to tividenofusp alfa (DNL310), including the ongoing COMPASS study and the timing and pathway for approval; and statements made by Denali's Chief Medical Officer. Actual results are subject to risks and uncertainties and may differ materially from those indicated by these forward-looking statements as a result of these risks and uncertainties, including but not limited to, risks related to: Denali's dependence on successful development of its BBB platform technology and TV-enabled product candidates; Denali's ability to initiate and enroll patients in its current and future clinical trials; Denali's ability to conduct or complete clinical trials on expected timelines; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; the potential for clinical trial results to differ from preclinical, early clinical, preliminary or expected results; the risk of significant adverse events, toxicities, or other undesirable side effects; the risk that results from early clinical biomarker studies will not translate to clinical benefit in late clinical studies; the risk that product candidates may not receive regulatory approval necessary to be commercialized; developments relating to Denali's competitors and its industry, including competing product candidates and therapies; Denali's ability to obtain, maintain, or protect intellectual property rights; and other risks and uncertainties. In light of these risks, uncertainties, and assumptions, the forward-looking statements in this press release are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Information regarding additional risks and uncertainties may be found in Denali's Annual and Quarterly Reports filed on Forms 10-K and 10-Q filed with the Securities and Exchange Commission (SEC) on February 28, 2024, and May 7, 2024, respectively, and Denali's future reports to be filed with the SEC. Denali does not undertake any obligation to update or revise any forward-looking statements, to conform these statements to actual results or to make changes in Denali's expectations, except as required by law.

Reference:

1. U.S. Food and Drug Administration (September 29, 2023): FDA Launches Pilot Program to Help Further Accelerate Development of Rare Disease Therapies. https://www.fda.gov/news-events/press-announcements/fda-launches-pilot-program-help-further-accelerate-development-rare-disease-therapies (Accessed June 3, 2024)

Investor and Media Contact:
Laura Hansen, PhD
Vice President, Investor Relations
(650) 452-2747
hansen@dnli.com

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