



Denali Therapeutics Announces Initiation of Phase 1b Study of EIF2B Activator DNL343 in ALS

September 9, 2021

— Investigational EIF2B activator approach has potential to be a first-in-class treatment for ALS —

SOUTH SAN FRANCISCO, Calif., Sept. 09, 2021 (GLOBE NEWSWIRE) -- [Denali Therapeutics Inc.](#) (NASDAQ: DNL1), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for neurodegenerative diseases, today announced that dosing recently commenced in a Phase 1b study of DNL343, its brain-penetrant small molecule activator of EIF2B, in participants diagnosed with amyotrophic lateral sclerosis (ALS).

ALS, often called Lou Gehrig's disease, refers to a group of progressive neurodegenerative diseases that affect nerve cells in the brain and spinal cord, leading to loss of voluntary muscle control and movement. At least 20,000 people in the United States are currently affected and approximately 5,000 individuals are newly diagnosed with ALS each year.

"Initiation of this Phase 1b study marks a significant milestone in the development of DNL343 for the potential treatment of people living with ALS," said Carole Ho, M.D., Denali's Chief Medical Officer. "Our preclinical and Phase 1 healthy volunteer data demonstrate activity of DNL343 on biomarkers believed to be highly relevant to ALS, and we look forward to sharing this data at an upcoming scientific conference. This Phase 1b study will help further characterize the safety and activity of DNL343 in participants with ALS for whom treatment options are a critical unmet medical need."

Denali plans to present the DNL343 Phase 1 healthy volunteer data at the 2021 Annual Northeast Amyotrophic Lateral Sclerosis (NEALS) Meeting on October 6, 2021.

About the Phase 1b study of DNL343 in ALS

The Phase 1b clinical trial (study number NCT05006352) is a multicenter, randomized, placebo-controlled, double-blind, 28-day study followed by an 18-month open-label extension, designed to evaluate the safety, pharmacokinetics, and pharmacodynamics of DNL343 in participants with ALS. Further information on the Phase 1b study can be accessed on the ClinicalTrials.gov website or by clicking [here](#).

About DNL343 and targeting EIF2B as a potential treatment for ALS

Modulation of EIF2B activity with DNL343 is a novel and targeted investigational approach with first-in-class potential for the treatment of ALS. EIF2B is an intracellular protein complex that regulates protein synthesis and is required for neuronal health and function. When neurons experience stress, as occurs in ALS, EIF2B activity is suppressed. This leads to impaired protein synthesis and results in the formation of "stress granules," which are thought to be a precursor of TDP-43 aggregation, a hallmark pathology in ALS. DNL343 is designed to activate EIF2B and thereby restore protein synthesis, disperse TDP-43 aggregates, and improve neuronal survival.

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 neurodegenerative 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 progress, business plans, business strategy, product candidates, planned preclinical studies and clinical trials and expected milestones; EIF2B activators as therapy for amyotrophic lateral sclerosis; plans, timelines and expectations related to DNL343, including its use as a potential treatment of people living with amyotrophic lateral sclerosis; 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: any and all risks to Denali's business and operations caused directly or indirectly by the evolving COVID-19 pandemic; risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's collaboration agreements; Denali's early stages of clinical drug development; Denali's and its partners' ability to complete the development and, if approved, commercialization of its product candidates; Denali's and its partners' ability to enroll patients in its ongoing and future clinical trials; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; Denali's and its partners' ability to conduct or complete clinical trials on expected timelines; the risk that preclinical profiles of Denali's product candidates may not translate in clinical trials; the potential for clinical trials or clinical trials of any other product candidates to differ from preclinical, preliminary or expected results; the uncertainty that product candidates will receive regulatory approval necessary to be commercialized; Denali's ability to continue to create a pipeline of product candidates or develop commercially successful products; Denali's ability to obtain, maintain, or protect intellectual property rights related to its product candidates;

implementation of Denali's strategic plans for its business, product candidates and blood-brain barrier platform technology; and other risks, including those described in Denali's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 4, 2021, Denali's Annual Report on Form 10-K filed with the SEC on February 26, 2021, and Denali's future reports to be filed with the SEC. The forward-looking statements in this press release are based on information available to Denali as of the date hereof. Denali disclaims any obligation to update any forward-looking statements, except as required by law.

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Source: Denali Therapeutics Inc.