Denali Therapeutics Announces DNL343 Interim Phase 1b Data in ALS and Entry into the HEALEY ALS Platform Trial

December 5, 2022 12:00 PM PST

- DNL343 demonstrated extensive blood-brain barrier penetration and robustly inhibited the integrated stress response pathway implicated in ALS
- Once-daily oral dosing with DNL343 for 28 days was generally well tolerated in participants with ALS
- The design phase for entry of DNL343 into a Phase 2/3 trial in the HEALEY ALS Platform Trial is underway

SOUTH SAN FRANCISCO, Calif., Dec. 05, 2022 (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 neurodegenerative diseases and lysosomal storage disorders, today announced interim results from a Phase 1b study of its eIF2B agonist, DNL343, in participants with amyotrophic lateral sclerosis (ALS). Once-daily oral dosing with DNL343 for 28 days was generally well tolerated and demonstrated extensive BBB penetration as well as robust inhibition of biomarkers associated with the integrated stress response (ISR) in blood samples from study participants. By inhibiting the ISR pathway, DNL343 is intended to prevent or slow disease progression associated with stress granule formation and TDP-43 aggregation, a hallmark pathology present in nearly all individuals with ALS. The Phase 1b results will be presented at the 33rd International Symposium on ALS/MND, which is being held virtually December 6-9, 2022. A copy of the poster presentation is available on Denali's website on the Investor & Media Relations section under the Events page. Denali also announced initiation of the design phase of a Phase 2/3 study for entry into the HEALEY ALS Platform Trial led by the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital (MGH) in collaboration with the Northeast ALS Consortium.

"These initial Phase 1b results with DNL343 in ALS are consistent with our previously reported Phase 1 healthy volunteer data and are an important milestone for the program," said Carole Ho, M.D., Chief Medical Officer at Denali. "The data continue to support late-stage development plans for DNL343, and we are excited to be collaborating with the HEALEY ALS Platform Trial team in our unified effort to advance potential treatment options for people living with ALS."

"ALS is a devastating progressive disorder with very few treatment options," said Merit Cudkowicz, M.D., M.Sc., principal investigator and sponsor of the HEALEY ALS Platform Trial, director of the Sean M. Healey & AMG Center for ALS, chief of the Department of Neurology at MGH, and the Julieanne Dorn Professor of Neurology at Harvard Medical School. "Given the strong collective data from the DNL343 program to date, we are looking forward to working with Denali to develop DNL343 for the HEALEY ALS Platform Trial, bringing us closer to our goal of finding more effective treatments for ALS through collaboration."

About the Phase 1b study in ALS
As previously announced, the Phase 1b study 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. Enrollment in the study is complete with 29 participants. An interim analysis was performed after 20 participants randomized to receive DNL343 or placebo had completed the double-blind period of the study. The open-label extension is ongoing. Further information on the study can be accessed at ClinicalTrials.gov.

In the interim analysis, DNL343 demonstrated dose-dependent increases in plasma concentrations and a long plasma half-life, supporting once-daily dosing. The mean ratio of drug in cerebrospinal fluid compared to unbound drug in plasma ranged from 1.02–1.23, suggesting that DNL343 effectively crosses the blood-brain barrier and is extensively distributed to the central nervous system. Robust inhibition of ISR was noted, as measured by attenuation of the ISR pathway biomarkers (ATF4 and *CHAC1*) in blood samples. DNL343 was generally well tolerated in participants with ALS in this study.

About the HEALEY ALS PLATFORM Trial
The HEALEY ALS Platform Trial is a large-scale collaborative effort made possible by contributions from patients and families, clinical trial sites, industry partners and research collaborators to evaluate multiple investigational therapies simultaneously with the goal of accelerating the development of potential new treatments for ALS. Therapeutic candidates that enter the platform trial are chosen by a group of expert ALS scientists and members of the Healey & AMG Center.

About the eIF2B activator DNL343
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, activation of the ISR pathway leads to suppression of eIF2B activity, resulting in impaired protein synthesis and formation of stress granules. Stress granules are thought to be a precursor of TDP-43 aggregation, which is a hallmark pathology in ALS. DNL343 is designed to activate eIF2B and thereby restore protein synthesis, disperse TDP-43 aggregates, and improve neuronal survival. DNL343 is an investigational therapeutic and has not been approved by any regulatory authority for any commercial use.

About Denali Therapeutics
Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the BBB for neurodegenerative diseases and lysosomal storage disorders. 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 plans, timelines and expectations related to DNL343, including the ongoing Phase 1b study and the initiation of the design phase of the Phase 2/3 study; the potential benefits of, likelihood of success of, and expectations related to Denali's collaboration with the HEALEY ALS Platform Trial; expectations regarding Denali's product candidates and the therapeutic and commercial potential of DNL343; and statements made by Denali's Chief Medical Officer and the HEALEY ALS Platform Trial's principal investigator. 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 transition to a late stage clinical drug development company; Denali's and its partners' ability to initiate, enroll patients in, conduct, and complete its ongoing and future clinical trials, including the ongoing Phase 1b study and upcoming Phase 2/3 study of DNL343, 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 of DNL343 to differ from preclinical, preliminary or expected results, including the initial Phase 1b results for DNL343; the risk of adverse events; risks related to Denali's collaborations; the risk that results from early clinical biomarker studies will not translate to clinical benefit in late clinical studies; the risk that DNL343 may not in the future receive regulatory approval as a treatment for ALS or other indications for which it is being developed; Denali's and its partners' ability to complete the development and, if approved, commercialization of its product candidates; Denali's and it's partners' ability to conduct or complete clinical trials on expected timelines; 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 BBB platform technology; and other risks. 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 most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 3, 2022, Denali's Annual Report on Form 10-K filed with the SEC on February 28, 2022, 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.

Investor Contact:
Laura Hansen, Ph.D.
(650) 452-2747
hansen@dnli.com

Media Contact:
Angela Salerno-Robin
(212) 445-8219
asalerno-robin@dna-comms.com

Source: Denali Therapeutics Inc.