Denali Therapeutics Announces Topline Results for Regimen G Evaluating eIF2B Agonist DNL343 in the Phase 2/3 HEALEY ALS Platform Trial

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- Primary endpoint of overall function (ALSFRS-R) and survival, and key secondary endpoints of muscle strength and respiratory function, were not met at 24 weeks
- Overall, DNL343 was found to be safe and well tolerated
- Additional analyses, including neurofilament light (NfL) and other fluid biomarkers, prespecified sub-group analyses and analyses from the active treatment extension period are expected later in 2025

SOUTH SAN FRANCISCO, Calif., Jan. 06, 2025 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (NASDAQ: DNLI) today announced topline results from an analysis of Regimen G of the Phase 2/3 HEALEY ALS Platform Trial evaluating eIF2B agonist DNL343 in the treatment of amyotrophic lateral sclerosis (ALS).

The study did not meet the primary endpoint of efficacy in slowing disease progression as compared with placebo. The primary endpoint was evaluated as change in disease severity over time as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) and survival through week 24. Key secondary endpoints, measuring muscle strength and respiratory function, were also not statistically different between the active and placebo groups at week 24.

For the primary analysis, a total of 186 participants who were randomized to receive DNL343 treatment were compared to 139 participants randomized to receive placebo in this regimen (n=63) or shared from a concurrently enrolling regimen (n=76).

Overall, DNL343 was found to be safe and well tolerated. Further analyses are anticipated later in 2025, including neurofilament light (NfL) and other fluid biomarkers, data from pre-specified subgroups, as well as extended findings from the active treatment extension period.

“Better treatment options for individuals with ALS are critically needed,” said Carole Ho, M.D., Chief Medical Officer of Denali Therapeutics. “We are deeply grateful to the study participants, investigators, and the broader community for their collective support of the HEALEY study, which has provided an efficient and innovative platform for evaluating the therapeutic potential of DNL343 in addressing this critical unmet need. We look forward to a more comprehensive analysis of the study results as additional analyses, including pre-specified subgroup analyses and treatment effects on NfL, become available later in 2025.”

“Though the initial top-line clinical results of this trial were not what we hoped, the data collected is valuable in helping to understand the next stage of ALS research,” said Merit Cudkowicz, MD, MSc, 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. “We have additional pre-specified subgroup analyses and biomarker work, including NfL, pending from this regimen, as well as long term efficacy data from participants who continued in the active treatment extension period. We remain deeply committed to fully understanding the effects of DNL343 in ALS and will further evaluate the data before determining next steps.”

About ALS

Amyotrophic lateral sclerosis (ALS) is the most prevalent adult-onset progressive motor neuron disease, affecting approximately 30,000 people in the U.S. and an estimated 500,000 people worldwide. ALS causes the progressive degeneration of motor neurons, resulting in muscle weakness and atrophy. There is an urgent need to understand the biology of ALS and to develop effective therapies.

About DNL343

DNL343 is a novel small molecule ALS therapeutic candidate that targets eIF2B, a central regulator of the integrated stress response (ISR). The ISR appears to be overactive in ALS, leading to the formation of stress granules containing TDP-43.[1,2] The buildup of TDP-43 is harmful and leads to neuronal degeneration. In preclinical data, inhibition of the ISR by DNL343 dissolves TDP-43 containing stress granules and decreases biomarkers of the ISR. Early clinical studies have demonstrated that once-daily oral dosing with DNL343 was generally well tolerated and exhibited extensive penetration of cerebrospinal fluid. In addition, robust inhibition of biomarkers associated with the ISR pathway was observed in blood samples from study participants. DNL343 is an investigational drug and its safety and efficacy profile has not yet been established. DNL343 has not been approved by any Health Authority for any use.

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. The platform trial is led by the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital (MGH) in collaboration with the Northeast ALS Consortium (NEALS).

Therapeutic candidates that enter the platform trial are chosen by a group of expert ALS scientists and members of the Healey & AMG Center.

About Denali Therapeutics

Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier for neurodegenerative diseases and lysosomal storage diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the blood-brain barrier 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 DNL343; the timing and availability of further data and analyses related to Regimen 3 of the Phase 2/3 HEALEY Platform Trial; and statements made by Denali's Chief Medical Officer and the principal investigator and sponsor of the HEALEY ALS Platform Trial. 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 without limitation, 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 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, preliminary or expected results; the risk of adverse events, toxicities, and 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 in the future receive regulatory approval necessary to be commercialized; 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 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 November 6, 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. Fang, MY et al. "Small-Molecule Modulation of TDP-43 Recruitment to Stress Granules Prevents Persistent TDP-43 Accumulation in ALS/FTD." *Neuron* 2019 Sep 4;103(5):802-819
2. Luan, W et al. "Early activation of cellular stress and death pathways caused by cytoplasmic TDP-43 in the rNLS8 mouse model of ALS and FTD." *Mol Psychiatry* 2023 Jun;28(6):2445-2461

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