Denali Therapeutics Announces Robust Reduction in Neurofilament Light (NfL) with DNL310 (ETV:IDS) Treatment in MPS II (Hunter Syndrome)

June 20, 2023

- Interim results demonstrate average reduction of 64% (p <0.001) from baseline in serum NfL after 2 years of dosing with DNL310 in Phase 1/2 study
- FDA has recommended assessment of NfL, a marker of neuroaxonal damage, as a possible biomarker in MPS II
- Additional interim data from the DNL310 Phase 1/2 study will be presented at the SSIEM symposium in August
- Management will host a webinar for analysts and investors at 8:30 a.m. Eastern Time today

SOUTH SAN FRANCISCO, Calif., June 20, 2023 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (NASDAQ: DNLI), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier for the treatment of neurodegenerative diseases and lysosomal storage diseases, today announced new interim results from the ongoing open-label, single-arm Phase 1/2 study of DNL310 (ETV:IDS) in children with MPS II (Hunter syndrome). Among the 13 participants who reached two years of treatment at the time of the interim analysis, a mean reduction of 64% (p<0.001) from baseline in serum neurofilament light (NfL) was observed. The U.S. Food and Drug Administration (FDA) recently recommended to Denali the assessment of NfL as an exploratory endpoint to assess its potential as a possible biomarker to assess diagnostic, prognostic, or therapeutic response in subjects with neuronopathic MPS II. DNL310 is an investigational brain-penetrant enzyme replacement therapy designed to address the behavioral, cognitive, and physical manifestations of MPS II. The global Phase 2/3 COMPASS study is ongoing.

“The serum NfL reduction in MPS II patients receiving longer term dosing with DNL310 is very promising, particularly in the context of DNL310’s ability to normalize CSF heparan sulfate, which is the primary substrate that is associated with neurodegeneration in MPS disorders,” said Joseph Muenzer, M.D., Ph.D., Bryson Distinguished Professor in Pediatric Genetics, University of North Carolina at Chapel Hill. “I look forward to seeing how CSF heparan sulfate and serum NfL could support approval to expedite treatment options for the MPS II community.”

Denali was the first to publish research on biomarkers downstream of heparan sulfate, including biomarkers of lysosomal and neuronal health, in MPS II[1] and has continued to explore biomarkers in the DNL310 clinical development program.

“These are impressive data and the first report of a robust reduction in NfL observed with any treatment in MPS II,” said Henrik Zetterberg, M.D., Ph.D., Professor and Chief Physician at the University of Gothenburg. “NfL is an established marker of neuroaxonal damage, which has demonstrated utility as a biomarker of therapeutic response in other neurodegenerative diseases such as CLN2, MS, SMA, and ALS.”

“The robust reduction and normalization of CSF heparan sulfate, and now the downstream reduction in NfL after treatment, are consistent with positive changes in clinical outcomes measures we have observed from interim analyses of the ongoing Phase 1/2 study,” said Carole Ho, M.D., Chief Medical Officer at Denali. “As we advance DNL310 as a potential treatment option for individuals living with MPS II, we look forward to ongoing engagement with the FDA and the MPS community.”

Additional interim data from the Phase 1/2 study of DNL310 will be highlighted in an oral presentation at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium 2023 in Jerusalem, Israel, August 29 – September 1, 2023.

Webinar for analysts and investors at 8:30 a.m. Eastern Time today

Denali will host a webinar for analysts and investors to present the interim NfL data from the Phase 1/2 study of DNL310. The webinar will begin at approximately 8:30 a.m. Eastern Time on Tuesday, June 20, 2023, and will be available on Denali’s corporate website on the Events page under the Investor & Media Relations section and can be accessed by following this link. An archived replay of the webinar will be available for at least 30 days following the event.

About MPS II (Hunter syndrome)

MPS II, also called Hunter syndrome, is a rare genetic disease that affects over 2,000 individuals, primarily males, world-wide, and leads to behavioral, cognitive, and physical symptoms ultimately resulting in shortened lifespan. MPS II is caused by mutations in the iduronate-2-sulfatase (IDS) gene, which leads to a deficiency of the IDS enzyme. Symptoms often begin emerging around age two and include physical complications, including organ dysfunction, joint stiffness, hearing loss and impaired growth, and neurocognitive symptoms with impaired development. The disease is characterized by a buildup of glycosaminoglycans (GAGs) in lysosomes — the part of the cell that breaks down materials including GAGs. The current standard of care enzyme replacement therapy partially treats the physical symptoms but does not cross the blood-brain barrier, and as a result, cognitive and behavioral symptoms experienced by the majority of patients with MPS II are not addressed. Therapies that address behavioral, cognitive, and physical manifestations of the disease are one of the greatest unmet needs for this community.

About DNL310 (ETV:IDS)

DNL310 is an investigational fusion protein composed of IDS fused to Denali's proprietary ETV, which is engineered to cross the blood-brain barrier via receptor-mediated transcytosis into the brain. Preclinical studies demonstrate that DNL310 delivers IDS to lysosomes, where it is needed to break down GAGs. DNL310 is engineered for broad delivery of IDS into cells and tissues throughout the body, including the brain 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.

Denali most recently reported (corporate press release dated February 22, 2023) interim Phase 1/2 results demonstrating positive changes across measures of exploratory clinical outcomes including VABS-II (adaptive behavior) and BSID-III (cognitive capabilities) scores and global impression scales over 49 weeks of treatment with DNL310. In addition, the interim data also suggested that DNL310 improved hearing, as assessed by auditory brainstem response testing. Additional biomarker data out to 49 weeks continued to demonstrate that DNL310 enabled rapid and sustained normalization of CSF heparan sulfate to normal healthy levels and improvement in lysosomal function biomarkers. Reduction in urine heparan sulfate and dermatan sulfate after switch from standard of care to DNL310 suggested additional sustained peripheral activity of DNL310. The safety profile of DNL310, with up to two years of treatment, remained consistent with standard of care.

Based on supportive clinical and preclinical data to date, Denali is conducting the Phase 2/3 COMPASS study, which is expected to enroll 54 participants with MPS II with and without neuronopathic disease. The participants will be randomized 2:1 to receive either DNL310 or idursulfase, respectively. Cohort A will include children ages 2 to 6 with neuronopathic disease; cohort B will include children ages 6 to 17 without neuronopathic disease.

The Phase 2/3 COMPASS study is being conducted globally in North America, South America, and Europe. 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 (NCT05371613) can be found here.

Families interested in learning more about Denali's efforts related to the discovery and development of therapeutics for the potential treatment of Hunter syndrome are invited to visit EngageHunter.com, the Denali Hunter syndrome community engagement website, an online destination for information on Denali's scientific approach in Hunter syndrome research and Denali's clinical trials.

DNL310 is an investigational product candidate and has not been approved by any health authority.

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 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 DNL310 and its therapeutic potential; the enrollment, timing, and availability and impact of data related to the ongoing Phase 2/3 COMPASS study and the open-label, single-arm Phase 1/2 study; the expectation and timing of DNL310 regulatory submissions and the potential to support registration; expectations regarding Denali's TV technology platform and the therapeutic potential of DNL310; the timing of future DNL310 presentations and webinars; and statements made by Joseph Muenzer, M.D., Ph.D., Henrik Zetterberg, M.D., Ph.D., and 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 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 of DNL310 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 DNL310 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 27, 2023, and May 8, 2023, 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.

References:

1. Bhalla A, et al. "Characterization of Fluid Biomarkers Reveals Lysosome Dysfunction and Neurodegeneration in Neuronopathic MPS II Patients." Int. J. Mol. Sci. 2020, 21, 5188.

Investor and Media Contact:

Laura Hansen, Ph.D.
Vice President, Investor Relations
(650) 452-2747
hansen@dnli.com

Source: Denali Therapeutics Inc.