Denali Therapeutics Announces New Data and Expansion of Its Blood-Brain Barrier (BBB)-Crossing Enzyme Replacement Therapy Programs at WORLDSymposium™

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- New data show additional improvement and stabilization in clinical outcomes in MPS II with 104 weeks of tividenofusp alfa (DNL310) treatment in the open-label, single-arm Phase 1/2 study; sustained normalization of CSF heparan sulfate and robust, sustained reduction in neurofilament light chain (NfL) observed
- Announcing initiation of dosing with DNL126 (ETV:SGSH) in Phase 1/2 study in MPS IIIA and new supportive data with MPS IIIA mice showing reductions in heparan sulfate correlated with improvements in cognitive function

SOUTH SAN FRANCISCO, Calif., Feb. 07, 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 diseases and lysosomal storage diseases, today announced new data presentations highlighting the broad potential of its BBB-crossing enzyme replacement therapies in development for the treatment of mucopolysaccharidoses (MPS). New clinical data on tividenofusp alfa (DNL310) in MPS II (Hunter syndrome) and mouse model data on DNL126 (ETV:SGSH) in MPS IIIA (Sanfilippo syndrome type A) are being presented this week at the 20th Annual WORLD*Symposium*™ in San Diego, California.

“It is exciting to see new clinical outcomes data, now up to two years of treatment with tividenofusp alfa,” said Joseph Muenzer, M.D., Ph.D., Bryson Distinguished Professor in Pediatric Genetics, University of North Carolina at Chapel Hill, who presented the Phase 1/2 data on tividenofusp alfa in MPS II. “The robust and sustained biomarker reductions, including NfL, and the effects on measures of behavior, cognition, hearing, liver volumes and growth indicate positive treatment effects in brain and somatic tissues. Denali’s BBB-crossing enzyme replacement approach has the potential to prevent cognitive and behavioral manifestations in MPS IIIA. Together with Denali and the MPS community, I am passionately advocating for the fastest path to approval to enable new treatment options for people living with MPS diseases.”

In addition, new data on somatic outcomes from the same study of tividenofusp alfa will be presented for the first time by Barbara Burton, M.D., Professor of Pediatrics, Genetics, Genomics and Metabolism at Feinberg School of Medicine in Chicago. The Phase 1/2 results demonstrate normalization of enlarged liver and spleen volumes and maintenance of normal growth compared to healthy boys in almost all participants. New two-year peripheral biomarker data demonstrate high magnitude and sustained reduction of urine heparan sulfate and dermatan sulfate, including in participants who switched from standard-of-care enzyme replacement therapy to tividenofusp alfa, suggesting enhanced peripheral activity. Tividenofusp alfa treatment continued to be generally well tolerated.

New MPS IIIA mouse model data on DNL126 will also be presented at the conference showing improvements in lysosomal and microglial morphology, neurodegeneration, and cognitive function. Treatment with DNL126 resulted in lowered heparan sulfate accumulation in the brain and in cerebrospinal fluid and improved cognitive function in adult MPS IIIA mice. A correlation between the levels of heparan sulfate and cognitive behavioral performance was observed. Denali also announced that dosing has begun in the Phase 1/2 study of DNL126 for the potential treatment of MPS IIIA.

“Our goal is to bring effective new medicines to MPS families as soon as possible,” said Carole Ho, M.D., Chief Medical Officer of Denali. “We are excited to present additional Phase 1/2 data demonstrating the potential for tividenofusp alfa to treat both brain and physical symptoms of MPS II disease, and we look forward to continued collaboration with the MPS community to complete enrollment in our global Phase 2/3 COMPASS study this year. We are also pleased to share that dosing has begun in the Phase 1/2 study of DNL126 for the potential treatment of MPS IIIA. We are driven by the urgent need of patients and families and will work with the community of scientists, physicians, advocates, and the FDA to find the fastest path to approval.”

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 responsible for the breakdown of the glycosaminoglycans (GAGs) heparan and dermatan sulfate in lysosomes. Symptoms often begin emerging around age two and include physical complications, including organ dysfunction, joint stiffness, hearing loss and impaired growth leading to short stature, and neurocognitive symptoms with impaired development. The disease is characterized by a buildup of 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 BBB, 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 tividenofusp alfa (DNL310)
Tividenofusp alfa (DNL310) is a fusion protein composed of 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
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. 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 can be found here.

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, ETV-enabled N-sulfoglucosamine sulfohydrolase (SGSH) replacement therapy designed to cross the BBB for the potential treatment of MPS IIIA. A Phase 1/2 study of DNL126 in MPS IIIA is ongoing; more information 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 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, the ongoing Phase 2/3 COMPASS study, and the open-label, single-arm Phase 1/2 study, including the continued recruitment of participants for the Phase 2/3 COMPASS study and the timing and availability of data for both studies; the potential for data from the ongoing DNL310 studies to support registration; expectations related to DNL126, the ongoing natural history study, and the ongoing Phase 1/2 study; expectations regarding the therapeutic potential of Denali's Transport Vehicle platform and DNL310; and statements made by Drs. Joseph Muenzer and Carole Ho. 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 27, 2023, and November 7, 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.

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