Denali Therapeutics Announces Presentations on Its Investigational Blood-Brain Barrier (BBB)-Crossing Enzyme Replacement Therapies at the Upcoming 2024 WORLDSymposium™

February 1, 2024 1:00 PM PST

SOUTH SAN FRANCISCO, Calif., Feb. 01, 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 upcoming presentations from its Enzyme Transport Vehicle (ETV) development programs, tividenofusp alfa (DNL310) and DNL126 (ETV:SGSH), to be given at the 20th Annual WORLD*Symposium* ™, which will be held February 4-9, 2024, in San Diego, California.

WORLD*Symposium* ™ Presentation Details on DNL310 and DNL126
Presentations on DNL310 will include new two-year data on clinical outcomes and previously presented data on biomarkers from the ongoing Phase 1/2 study in MPS II. In addition, an oral presentation will highlight data from preclinical studies of DNL126 in an MPS IIIA mouse model. The presentation schedule at WORLD*Symposium* ™ is as follows:

Title: Interim Analysis of a Phase 1/2 Study of Weekly Intravenous DNL310 (Brain-Penetrant Enzyme Replacement Therapy) in Mucopolysaccharidosis Type II
Session: Clinical Applications Platform Presentations
Date: Wednesday, February 7, 2024
Time: 9:00 AM Pacific Time

Title: Somatic Outcomes in a Phase 1/2 Study of Weekly Intravenous DNL310 (Brain-Penetrant Enzyme Replacement Therapy) in Mucopolysaccharidosis Type II (Poster #43)
Session: Clinical Applications – Poster Session III
Date: Wednesday, February 7, 2024
Time: 3:00 PM - 5:00 PM Pacific Time

Title: DNL310 Phase 1/2 Case Study Demonstrates Properties of Raw, Standard and Growth Scale Scores for Adaptive Behavior Scales (Poster #80)
Session: Contemporary Forum – Poster Session IV
Date: Thursday, February 8, 2024
Time: 3:00 – 5:00 PM Pacific Time

Title: DNL310 Normalizes Primary Storage Substrates, Corrects Biomarkers of Lysosomal Dysfunction and Reduces Biomarkers of Neuronal Injury (Neurofilament Light Chain) in MPS II: 2-Year Interim Analysis of a Phase 1/2 Study (Poster #34)
Session: Contemporary Forum – Poster Session IV
Date: Thursday, February 8, 2024
Time: 3:00 – 5:00 PM Pacific Time

Title: ETV:SGSH, a Brain-Penetrant Enzyme Transport Vehicle for SGSH, Improves Lysosomal and Microglial Morphology, Degeneration and Cognitive Behavior in MPS IIIA Mice
Session: Contemporary Forum Platform Presentations
Date: Thursday, February 8, 2024
Time: 1:00 PM Pacific Time

Denali is also participating in or sponsoring the following events being held at the WORLD*Symposium* ™ :

Title: 3rd Annual Robert J. Gorlin Symposium – Beyond the Blood Brain barrier: Strategies for Treating the CNS
Course Director: Jeanine R. Jarnes, PharmD, MSc, BCOP, BCPS
Date: Tuesday, February 6, 2024
Time: 5:15 – 7:30 PM Pacific Time

Title: From Prevailing to Pioneering – Current and Emerging Biomarkers in Neurodegenerative Lysosomal Diseases
Date: Wednesday, February 7, 2024
Time: 5:15 – 6:15 PM Pacific Time

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 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 an investigational fusion protein composed of IDS fused to Denali's proprietary ETV, which is engineered to cross the BBB via receptor-mediated transcytosis into the brain. Preclinical studies demonstrate that DNL310 delivers IDS to lysosomes in the brain, 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. 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 conducting the Phase 2/3 COMPASS study of DNL310, which is expected to enroll 54 participants with MPS II with and without neuronopathic disease. The participants are randomized 2:1 to receive either 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. Among these, Type A is the most common and 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; 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 (TV) Platform

The BBB is essential in maintaining the brain's microenvironment and protecting it from harmful substances and pathogens circulating in the bloodstream. Historically, the BBB 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 TV platform is a proprietary technology designed to effectively deliver large therapeutic molecules such as antibodies, enzymes, proteins, and oligonucleotides across the BBB after intravenous administration. The TV technology is based on engineered Fc domains that bind to specific natural transport receptors, such as transferrin receptors, which are expressed at the BBB and deliver the TV and its therapeutic cargo to the brain through receptor-mediated transcytosis. In animal models, antibodies and enzymes engineered with the TV 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 (BBB) for the treatment of neurodegenerative diseases and lysosomal storage 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 planned presentations and events at the 2024 WORLD *Symposium* ™; Denali's plans and expectations related to DNL310, the ongoing Phase 2/3 COMPASS study, and the open-label, single-arm Phase 1/2 study, including the expectation that the

studies may support registration; expectations related to DNL126 and the ongoing natural history study; and expectations related to Denali's TV technology platform and its therapeutic efficacy. 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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Source: Denali Therapeutics Inc.