Denali Therapeutics Announces Presentations on Enzyme Transport Vehicle (ETV) Development Programs for MPS Diseases at the Upcoming WORLDSymposium™

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SOUTH SAN FRANCISCO, Calif., Feb. 15, 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 upcoming presentations from Enzyme Transport Vehicle (ETV) development programs, DNL310 (ETV:IDS) and DNL126 (ETV:SGSH), to be given at the 19th Annual WORLD*Symposium* ™, which will be heldFebruary 22-26, 2023, in Orlando, Florida.

DNL310 is an investigational, ETV-enabled, brain-penetrant enzyme replacement therapy designed to address the behavioral, cognitive, and physical manifestations of MPS II (Hunter syndrome). Denali is evaluating DNL310 in the global Phase 2/3 COMPASS study, which is enrolling participants with MPS II in North America, South America, and Europe, and in an open-label, single-arm Phase 1/2 study. DNL126 is Denali's second most advanced ETV-enabled program in development for the potential treatment of MPS IIIA (Sanfilippo syndrome type A) for which Denali plans to submit an Investigational New Drug (IND) application in the first half of 2023.

Presentations on DNL310 will include new interim data on biomarkers, safety, exploratory clinical outcomes and an analysis of toileting ability from the ongoing Phase 1/2 study as well as the Phase 2/3 COMPASS study design. In addition, another 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 key clinical outcomes from a phase 1/2 study of weekly intravenous DNL310 (brain-penetrant enzyme replacement therapy) in MPS II
Session: Clinical Applications Platform Presentations
Date: Friday, February 24, 2023
Time: 9:00 AM Eastern Time

Title: Interim analysis of key clinical outcomes from a phase 1/2 study of weekly intravenous DNL310 (brain-penetrant enzyme replacement therapy) in MPS II (Poster #248)
Session: Clinical Applications – Poster Session V
Date: Friday, February 24, 2023
Time: 3:00 PM - 4:00 PM Eastern Time

Title: COMPASS, A double-blinded randomized phase 2/3 study of the efficacy and safety of intravenous DNL310 (brain-penetrant enzyme replacement therapy) in MPS II (Poster #13)
Session: Contemporary Forum – Poster Session VII
Date: Saturday, February 25, 2023
Time: 3:00 – 4:00 PM Eastern Time

Title: DNL310 normalizes primary storage substrates and biomarkers of lysosomal dysfunction in neuronopathic MPS II: 2-year interim analysis of a phase 1/2 study (Poster #48)
Session: Contemporary Forum – Poster Session VII
Date: Saturday, February 25, 2023
Time: 3:00 – 4:00 PM Eastern Time

Title: DNL310-treated study participants with MPS II show improvements in toileting abilities
Session: Contemporary Forum Poster Presentations
Date: Saturday, February 25, 2023
Time: 4:00 – 5:00 PM Eastern Time

Title: ETV:SGSH, a brain-penetrant enzyme transport vehicle for SGSH, corrects heparan sulfate accumulation, lysosomal lipid storage and inflammation in MPS IIIA mouse brain
Session: Contemporary Forum Platform Presentations
Date: Saturday, February 25, 2023
Time: 8:00 AM Eastern Time
PDFs of the poster presentations will be made available on Denali's corporate website under the Investor Events section on February 22, 2023, at approximately 3:00 PM Eastern Time. PDFs of the oral presentations will be posted on Denali's corporate website under the Investor Events section on the corresponding date and time of the presentation.

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 physical, cognitive, and behavioral 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 Hunter syndrome 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. In March 2021, the U.S. Food and Drug Administration granted Fast Track designation to DNL310 for the treatment of patients with Hunter syndrome. 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 DNL310 Phase 2/3 COMPASS study

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 can be found here.

About DNL126 (ETV:SGSH) and MPS IIIA (Sanfilippo syndrome type A)

MPS IIIA, 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. DNL126 is an investigational, ETV-enabled, brain-penetrant SGSH replacement therapy designed to address the behavioral, cognitive and physical manifestations of MPS IIIA.

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 expectation that it is a potentially registrational trial; plans, timelines, and expectations

related to DNL126, including the expectation and timing of potential regulatory submissions; expectations regarding Denali's TV technology platform, the therapeutic potential of DNL310 and DNL126, and Denali's TV platform. 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: risks to Denali's business and operations caused directly or indirectly by the COVID-19 pandemic; Denali's early stages of clinical drug development; 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 DNL310 and DNL126 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 28, 2022, and November 3, 2022, 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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