Denali Therapeutics Announces New Interim Data from Phase 1/2 Study of DNL310 (ETV:IDS) in MPS II (Hunter Syndrome) at SSIEM 2022

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- Additional one-year data continue to show rapid and sustained normalization to healthy levels of CSF heparan sulfate and improvements in biomarkers of lysosomal function consistent with durable central nervous system activity
- Safety profile, now with up to 85 weeks of dosing, continues to be similar to standard of care
- One-year exploratory outcomes data from clinician and caregiver global impression scales of change suggest that the majority of participants in the Phase 1/2 study improved or stabilized compared to baseline
- Phase 2/3 COMPASS study is actively enrolling

SOUTH SAN FRANCISCO, Calif., Aug. 31, 2022 (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 neurodegenerative diseases and lysosomal storage disorders, today announced new interim results from a Phase 1/2 trial of DNL310 (ETV:IDS) in MPS II (Hunter syndrome). DNL310 is an investigational, brain-penetrant enzyme replacement therapy designed to address the cognitive, behavioral, and physical manifestations of Hunter syndrome. The data were presented at the 2022 Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium in Freiburg, Germany, by Joseph Muenzer, M.D., Ph.D., Bryson Distinguished Professor in Pediatric Genetics, University of North Carolina at Chapel Hill.

“The achievement of healthy normal levels of heparan sulfate in all participants in the Phase 1/2 study, including those with high pre-existing anti-iduronate-2 sulfatase antibodies, was also accompanied in most participants by improvement or stabilization in clinical symptoms and function as reported by both clinicians and caregivers,” said Carole Ho, M.D., Chief Medical Officer at Denali. “These latest interim data continue to differentiate DNL310 and demonstrate sustained effects on key MPS II disease biomarkers as well as a safety profile similar to standard of care. We are actively engaged in enrolling our Phase 2/3 COMPASS study in which we aim to demonstrate a meaningful impact for children with Hunter syndrome and their families.”

Dr. Muenzer added: "We have not previously seen reductions in CSF heparan sulfate to normal levels with any therapy, suggesting that we may see long-term cognitive stabilization with DNL310 in a population destined to have CNS decline. Furthermore, normal levels of CSF heparan sulfate were observed even in participants who entered the study with high levels of anti-drug antibodies against idursulfase. I am excited for the Phase 2/3 COMPASS study to continue to explore the potential of DNL310 as a treatment for the entire MPS II patient population.”

The presentation at SSIEM included data from 27 participants enrolled in the Phase 1/2 trial with data available as of the data cut off on March 22, 2022. All but one participant has neuronopathic MPS II, and the median age was 5 years (range 2 to 12). Participants received weekly intravenous doses of DNL310 starting on day 1 of the study, with no wash-out period for those switching from idursulfase. Earlier interim results from the Phase 1/2 study were presented at WORLD*Symposium*™2022 (link to corporate press release). A copy of the presentation is available on Denali’s website on the Investor & Media Relations section under the Events page. Key results are summarized below.

Data continue to show rapid and sustained reduction of relevant central nervous system (CNS) and peripheral biomarkers to normal healthy levels

Data from additional participants in the Phase 1/2 study continue to show rapid and sustained reduction of relevant CNS and peripheral biomarkers to normal healthy levels. Rapid normalization of cerebrospinal fluid (CSF) heparan sulfate levels was observed in most patients after 4 to 6 weekly intravenous doses of DNL310. All participants approached normal CSF heparan sulfate levels by week 24 and this was sustained in all participants who reached week 49 (89% reduction from baseline), including in two children with preexisting high levels of anti-iduronate-2-sulfatase antibodies.

Results also continued to demonstrate normalization of lysosomal lipid biomarkers in CSF, which is consistent with improved lysosomal function. At week 24, the mean decline in levels of the gangliosides GM2 and GM3 was 63% and 52%, respectively, which was sustained at week 49.

After switching from idursulfase to DNL310, a mean decline from baseline of 84% and 88% was observed for heparan sulfate and dermatan sulfate biomarkers in the urine, respectively, at week 49, suggesting DNL310 has added peripheral activity over approved enzyme replacement therapy.

One-year, exploratory, open-label clinical outcomes data suggest improvement or stabilization in the majority of Phase 1/2 study participants

One-year exploratory clinical outcomes data from the Phase 1/2 study were presented from Clinician Global Impression Scales of Change (CGI-C) and Caregiver Global Impression Scales of Change (CaGI-C) for the first time. These are standardized assessment scales used to measure change and modified to measure overall MPS II symptoms and specific domains impacted by Hunter syndrome, including communication, social skills, daily living skills, problematic behavior, and physical abilities. For participants with assessments at week 49, most demonstrated improvement or stabilization across all domains since entering the Phase 1/2 study.

Safety profile of DNL310, now with up to 85 weeks of dosing, remains similar to standard of care

The safety profile of DNL310 with up to 85 weeks of dosing remains similar to standard of care. The most frequent treatment-emergent adverse events (TEAEs) were infusion related reactions (IRRs). IRR frequency and severity decreased with continued dosing, demonstrating tolerance to dosing with DNL310. There were no treatment withdrawals or study discontinuations due to TEAEs. The study continues without modification following recommendation by an independent data monitoring committee in April 2022.

About Hunter Syndrome

Hunter syndrome, also called MPS II, is a rare genetic disease that affects over 2,000 individuals, primarily males, world-wide, and leads to physical, cognitive, and behavioral symptoms. Hunter syndrome 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 cognitive, behavioral, and physical manifestations of the disease are one of the greatest unmet needs for this community.

About DNL310

DNL310 is an investigational fusion protein composed of IDS fused to Denali's proprietary Enzyme Transport Vehicle (ETV), which is engineered to cross the blood-brain barrier via receptor-mediated transcytosis into the brain. 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 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 Hunter syndrome 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 designed to support registration of DNL310 for the treatment of MPS II. More information about the COMPASS study 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.

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 the EngageHunter.com Website

EngageHunter.com — the Denali Hunter syndrome community engagement website — is an online destination for emerging information on Denali's scientific advances in Hunter syndrome research and Denali's clinical trials. Visitors who register on the Engage Hunter website will receive updates on Denali's research and future Denali investigational studies. EngageHunter.com is

intended for U.S. audiences.

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. 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 the DNL310 ongoing Phase 1/2 study, plans regarding the timing and structure of, and expectations regarding enrollment in, the Phase 2/3 COMPASS study, including the expectation that it is potentially a registrational trial, expectations regarding Denali's Transport Vehicle technology and platform, the therapeutic potential of DNL310 and Denali's Transport Vehicle platform, and statements made by Denali's Chief Medical Officer and Dr. Joseph Muenzer. 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 early stages of clinical drug development; Denali's ability to complete the development and, if approved, commercialization of DNL310 on expected timelines; Denali's ability to initiate and enroll patients in the Phase 2/3 COMPASS study of DNL310 and other future clinical trials; 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, early clinical, preliminary or expected results; Denali's ability to continue dose escalation in the Phase 1/2 study of DNL310; the risk of significant adverse events, toxicities or other undesirable side effects related to DNL310; whether DNL310 will impact downstream biomarkers of neurodegeneration; the risk that results from early clinical biomarker studies will not translate to clinical benefit in late clinical studies; the risk that early clinical benefits will not continue to stabilize or improve with respect to clinical symptoms and function; the risk that DNL310 may not receive regulatory approval as a treatment for Hunter syndrome 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 related to DNL310; implementation of Denali's strategic plans for its business, product candidates and blood-brain barrier platform technology, including DNL310; 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 August 8, 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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