Denali Therapeutics Announces New Interim Data from DNL310 Phase 1/2 Study for MPS II and DNL126 Preclinical Data for MPS IIIA at WORLDSymposium™

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- Over 49 weeks of DNL310 (ETV:IDS) treatment in the Phase 1/2 study, positive changes across measures of exploratory clinical outcomes including VABS-II (adaptive behavior) and BSID-III (cognitive capabilities) scores and global impression scales were observed
- Interim Phase 1/2 data also suggest that DNL310 improves hearing, as assessed by auditory brainstem response testing
- Additional biomarker data out to 49 weeks continue to demonstrate that DNL310 enables rapid and sustained normalization of CSF heparan sulfate to normal healthy levels and improvement in lysosomal function biomarkers
- DNL310 safety profile, now with up to two years of treatment, remains consistent with standard of care
- Preclinical data on DNL126 (ETV:SGSH) support planned submission of investigational new drug (IND) application

SOUTH SAN FRANCISCO, Calif., Feb. 22, 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), including data from additional participants and up to 104 weeks of treatment. DNL310 is an investigational brain-penetrant enzyme replacement therapy designed to address the behavioral, cognitive, and physical manifestations of MPS II. The interim Phase 1/2 data are being presented at the 19th Annual WORLD*Symposium*™in Orlando, Florida, February 22-26, 2023.

“We continue to see sustained reductions in CSF heparan sulfate to normal levels in most individuals not previously seen with any other therapy. Furthermore, over 49 weeks, DNL310 treatment is associated with positive changes across measures of adaptive behavior and cognition, global impression, and improvements in measures of hearing function,” said Joseph Muenzer, M.D., Ph.D., Bryson Distinguished Professor in Pediatric Genetics, University of North Carolina at Chapel Hill. “As the study progresses and enrollment continues for the global Phase 2/3 COMPASS study, I am excited to learn more about the potential of DNL310 to offer meaningful benefit for the entire MPS II patient population."

“We are excited to share new interim analyses from the Phase 1/2 study, including data that suggests hearing improves within a year with DNL310 treatment in participants previously treated with idursulfase,” said Carole Ho, M.D., Chief Medical Officer at Denali. “The consistency of the strong biomarker data and positive trends in behavior, cognition, global impression data, and hearing, with a safety profile consistent with standard of care, suggest robust central nervous system and peripheral activity of DNL310. These data support continued recruitment in the Phase 2/3 COMPASS study. Additionally, we aim to apply our learnings more broadly to address high unmet need for individuals living with other MPS diseases.”

The oral presentation to be given on February 24, 2023, at the WORLD*Symposium*™will include data as of the September 2022 data cut off from the 28 participants enrolled in the Phase 1/2 study of DNL310. All but one participant has neuronopathic MPS II, and the median age at enrollment 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. Key interim results are summarized below:

- Exploratory clinical outcomes data from Vineland Adaptive Behavior Scales (VABS)-II and Bayley Scales of Infant and Toddler Development (BSID)-III assessments were reported for the first time and positive mean changes in raw scores over one year with DNL310 treatment relating to adaptive behavior and cognitive skill gains were observed, respectively. These raw score results are consistent with previously reported one-year findings from the Clinician Global Impression Scales of Change and Caregiver Global Impression Scales of Change, showing that most participants demonstrated improvement or stabilization across all domains at week 49 of study treatment.
- Hearing, as assessed by auditory brainstem response (ABR) testing, numerically improved over time after initiation of DNL310 across all frequencies. At week 49, ABR thresholds showed statistically significant improvements across three of the four frequencies, with a trend toward greater improvement at higher frequencies.
- The data continue to demonstrate that DNL310 enables rapid and sustained normalization of heparan sulfate in cerebrospinal fluid (CSF) with mean reductions from baseline of 91% and 90% at weeks 24 and 49, respectively. Normalization of CSF heparan sulfate was observed even in participants with high levels of preexisting anti-iduronate-2-sulfatase antibodies.
- Sustained reduction of lysosomal lipid biomarkers in CSF was also observed, which is consistent with improved lysosomal

function. At week 24, the mean decline in levels of gangliosides GM2, GM3, and glucosylsphingosine lipids were 64%, 54%, and 57%, respectively, which was sustained at week 49 (63%, 49%, and 48%, respectively).

- After switching from idursulfase to DNL310, a mean decline from baseline of 85% and 89% 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.

- The safety profile of DNL310 remains consistent with standard of care, now with data up to two years of treatment with DNL310. The most frequent treatment-emergent adverse events were infusion related reactions, which decreased in frequency and severity with continued dosing.

- An independent data monitoring committee met in October 2022 and recommended that the study may continue without modifications.

A PDF of the Phase 1/2 poster will be available on Denali's website on the Events page of the Investor section today.

A second oral presentation to be given on Saturday, February 25, 2023, will highlight preclinical data on DNL126 (ETV:SGSH), Denali's second most advanced ETV-enabled program. DNL126 is an investigational, brain-penetrant N-sulfoglucosamine sulfohydrolase (SGSH) replacement therapy designed to address the behavioral, cognitive, and physical manifestations of MPS IIIA (Sanfilippo syndrome Type A). Denali plans to submit an IND application for DNL126 in the first half of 2023. A PDF of the oral presentation will be available on Saturday, February 25, 2023, at 8:00 a.m. Eastern Time on the Events page of the Investor section of Denali's website.

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

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. 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 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.

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 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 MPS IIIA (Sanfilippo Syndrome)

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 (NCT05523206) of biomarkers and adaptive behavior in MPS IIIA is ongoing and 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. 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; and statements made by Dr. Joseph Muenzer 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 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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