The New England Journal of Medicine Publishes Phase 1/2 Study of Denali Therapeutics' Tividenofusp Alfa (DNL310) for Hunter Syndrome (MPS II)

December 30, 2025

- *Tividenofusp alfa treatment showed reduction and normalization in key disease biomarkers, stabilization or improvement in clinical endpoints including adaptive behavior, cognition and hearing, and normalization of liver volume*
- *Most common treatment-related adverse events were infusion-related reactions, which decreased with continued use*
- *Tividenofusp alfa is an investigational, next-generation enzyme replacement therapy engineered to cross the blood-brain barrier*
- *Biologics License Application for tividenofusp alfa is under FDA Priority Review, with Prescription Drug User Fee Act (PDUFA) date of April 5, 2026*

SOUTH SAN FRANCISCO, Calif., Dec. 30, 2025 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (Nasdaq: DNLI) today announced the publication of results from the open-label Phase 1/2 clinical trial of its investigational, next-generation enzyme replacement therapy (ERT), tividenofusp alfa (DNL310), for the treatment of Hunter syndrome (mucopolysaccharidosis type II, or MPS II) in the January 1, 2026 issue of *The New England Journal of Medicine*. The U.S. Food and Drug Administration (FDA) is conducting a Priority Review of the Biologics License Application (BLA) for tividenofusp alfa, which is supported by these data and for which Denali is seeking accelerated approval. A decision by the FDA on the tividenofusp alfa BLA is expected by April 5, 2026.

MPS II is a life-limiting lysosomal storage disease caused by a deficiency in the iduronate 2-sulfatase (IDS) enzyme, which is needed to break down complex sugars called glycosaminoglycans (GAGs). In individuals with MPS II, GAGs build up in cells throughout the body, including the brain, resulting in progressive damage to organs and tissues starting at a young age. MPS II occurs along a spectrum of disease severity, with approximately two-thirds of individuals developing progressive neurocognitive decline (neuronopathic MPS II). Current therapies do not cross the blood-brain barrier and therefore lack the potential to address the impact of the disease on cognitive abilities and behavior.

"There is an urgent need for new treatment options to address the full spectrum of Hunter syndrome, which can include severe cognitive and motor deficits such as losing the ability to hear, speak and walk," said Joseph Muenzer, M.D., Ph.D., lead investigator of the Phase 1/2 study, Director of the Muenzer MPS Research and Treatment Center and the Bryson Distinguished Professor in Pediatric Genetics at the University of North Carolina at Chapel Hill. "The Phase 1/2 data demonstrate that treatment with the brain-penetrant enzyme replacement therapy tividenofusp alfa substantially reduced central nervous system and peripheral biomarkers of substrate accumulation and neuronal injury, with the potential for improving clinical outcomes in MPS II. This novel treatment could have a profound impact for individuals and families living with this devastating disease."

Tividenofusp alfa is composed of IDS fused to Denali's TransportVehicle™ platform and is engineered to cross the blood-brain barrier, aiming to treat neurological manifestations of MPS II in addition to physical symptoms. The FDA has granted Rare Pediatric Disease Designation and Breakthrough Therapy Designation to tividenofusp alfa.

"Our investigational treatment, tividenofusp alfa, has the potential to become the first FDA-approved enzyme replacement therapy designed to treat the whole body, including the brain. We are excited by the clinical trial data showing that after treatment with tividenofusp alfa, the majority of participants had normalization of heparan sulfate levels in both cerebrospinal fluid and urine to levels in the range observed in children unaffected by this disease," said Peter Chin, M.D., Acting Chief Medical Officer and Head of Development of Denali Therapeutics. "We are deeply thankful to the individuals and families, clinical investigators and their teams contributing to the efforts to improve treatment options for the MPS community. We are committed to advancing and preparing for potential availability of tividenofusp alfa for individuals with Hunter syndrome."

"These data further validate our TransportVehicle as a platform with the potential to establish a new class of medicines that leverage natural transport mechanisms, such as the transferrin receptor (TfR), to enable and enhance delivery of biotherapeutics throughout the body, including the brain," said Ryan Watts, Ph.D., Chief Executive Officer of Denali Therapeutics. "Tividenofusp alfa would be the first FDA-approved TfR-enabled medicine specifically designed to cross the blood-brain barrier. In addition to evaluating our TransportVehicle to enable enzyme replacement across lysosomal storage disorders and neurodegenerative diseases, we are pursuing the potential of the platform to deliver antibodies and oligonucleotides for diseases that impact the brain."

Tividenofusp Alfa Phase 1/2 Trial Results

The primary objective of the Phase 1/2 study was safety and tolerability, and secondary objectives evaluated central nervous system and peripheral effects of tividenofusp alfa by measuring the GAG heparan sulfate (HS) in cerebrospinal fluid (CSF) and urine, adaptive behavior and liver volume. The study evaluated treatment in 47 ERT-naïve (n=15) and previously treated (n=32) study participants (aged 0.3–13 [median, 5] years), ranging from less severe to severe disease variants. Safety and tolerability data were consistent with previously reported results from this Phase 1/2 trial. The most common treatment-related adverse events were infusion-related reactions, which decreased in incidence with continued use. Results from key secondary endpoints are:

- Mean CSF levels of HS, the primary substrate found in high levels in the brain of individuals with MPS II, were reduced from baseline by 91% (95% CI, 90% to 92%; N=44) at Week 24 and maintained through Week 153 (92%; 95% CI, 90% to 93%; N=16). At Week 24, 93% of study participants reached levels within the range of children without MPS II.
- Mean urine HS levels were reduced by 88% (95% CI, 85% to 90%; N=40) from baseline at Week 24 and maintained through Week 153 (91%; 95% CI, 87% to 94%; N=10). At Week 24, 58% of participants reached levels in the range of children without MPS II.
- Serum neurofilament light (NfL) chain levels, a well-established biomarker of neuronal injury and an exploratory endpoint of the study, were reduced by 21% (95% CI, 5% to 35%; N=34) from baseline at Week 49. At Week 153, NfL was reduced by 76% (95% CI, 68% to 82%; N=13), and 85% of participants reached levels within the range of children without MPS II.
- Clinical results included normalization in liver volume after 24 weeks, improvement in hearing thresholds across tested frequencies, and skill gains in most participants on measures of adaptive behavior and cognition.

About Tividenofusp Alfa

Tividenofusp alfa (DNL310) is composed of the iduronate 2-sulfatase (IDS) enzyme fused to Denali's proprietary TransportVehicle™ (TV) platform, designed to deliver IDS into the brain and the body, with the goal of addressing behavioral, cognitive and physical symptoms of Hunter syndrome (MPS II). In addition to Rare Pediatric Disease Designation and Breakthrough Therapy Designation, the U.S. Food and Drug Administration has granted Fast Track and Orphan Drug designations to tividenofusp alfa for development in the treatment of MPS II. The European Medicines Agency has granted Priority Medicines designation to tividenofusp alfa.

Denali is conducting the Phase 2/3 COMPASS study in participants with MPS II in North America, South America and Europe to support global approval. Participants are randomized 2:1 to receive either tividenofusp alfa or idursulfase, respectively. More information about the COMPASS study can be found here.

Tividenofusp alfa is an investigational therapeutic and has not been approved for use by any Health Authority.

About Hunter Syndrome (MPS II)

Hunter syndrome, also known as MPS II, is a rare genetic lysosomal storage disease caused by mutations in the iduronate-2-sulfatase (IDS) gene. This results in a deficiency of the IDS enzyme, which is responsible for breaking down glycosaminoglycans (GAGs) such as heparan sulfate and dermatan sulfate. The accumulation of GAGs leads to progressive damage in multiple organs and tissues, including the brain. Symptoms of Hunter syndrome include developmental delays, cognitive decline, behavioral abnormalities and physical complications such as joint stiffness, hearing loss and organ dysfunction. Current standard-of-care enzyme replacement therapies do not cross the blood-brain barrier and therefore do not address the neurological symptoms of the disease. There is a significant unmet need for therapies that address both the central nervous system (CNS) and peripheral manifestations of Hunter syndrome.

About the Denali TransportVehicle ™ Platform

The blood-brain barrier (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 TransportVehicle ™ (TV) platform is a proprietary technology designed to effectively deliver large therapeutic molecules such as antibodies, enzymes and oligonucleotides throughout the whole body, including the brain, by crossing the BBB after intravenous administration. The TV platform is based on engineered Fc domains that bind to specific natural transport receptors, such as transferrin receptor and CD98 heavy chain amino acid transporter, 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 platform demonstrate more than 10- to 30-fold greater brain exposure than similar antibodies and enzymes without this technology. Oligonucleotides engineered with the TV platform demonstrate more than a 1,000-fold greater brain exposure in primates than systemically delivered oligonucleotides 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. The TV platform has been clinically validated and three TV-enabled programs are currently in clinical development.

About Denali Therapeutics

Denali Therapeutics is a biotechnology company pioneering a new class of biotherapeutics designed to cross the blood-brain barrier using its proprietary TransportVehicle™ platform. With a clinically validated delivery platform and a growing portfolio of therapeutic candidates across all stages of development, Denali Therapeutics is advancing toward its goal of delivering effective medicines to transform the lives of people living with neurodegenerative, lysosomal storage and other serious diseases.

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, plans, timelines and expectations related to tividenofusp alfa and Denali's TransportVehicle platform; expectations regarding the treatment impact, efficacy and safety of tividenofusp alfa; the timing of the PDUFA action date and expectations regarding the adequacy of the

Phase 1/2 or the Phase 2/3 COMPASS trial results to support regulatory review and achieving approvals from the FDA, EMA or other global regulatory agencies; plans to conduct development and commercialization activities, including the size of the potential market, the number of patients likely to be treated with tividenofusp alfa and the timing and likelihood of commercial launch; expectations for ongoing communications with the FDA; and statements made by Denali's Acting Chief Medical Officer and Head of Development and Chief Executive Officer. Actual results may differ materially from those expressed or implied by these forward-looking statements due to a variety of risks and uncertainties. These include, but are not limited to, uncertainties related to the FDA's policies and accelerated approval program, including risks that the PDUFA action date may be extended, the FDA may ultimately determine not to approve tividenofusp alfa or the BLA in its present form or at all, and the FDA may not grant Denali a Priority Review Voucher upon approval of the BLA; risks arising from adverse economic conditions and their impact on Denali's business and operations; the possibility of events or changes that could lead to the termination of Denali's collaboration agreements; challenges associated with Denali's transition to a late-stage clinical drug development and commercial company; the ability of Denali and its collaborators to complete the development and, if approved, the commercialization of product candidates; difficulties in patient enrollment for ongoing and future clinical trials; whether the current ongoing trials have been powered sufficiently to demonstrate approvability to regulatory agencies; reliance on third-party manufacturers and suppliers for clinical trial materials; dependence on the successful development of Denali's blood-brain barrier platform technology and related programs; potential delays or failures in meeting expected clinical trial timelines; the risk that promising preclinical profiles may not be replicated in clinical settings; discrepancies between preclinical, early-stage or preliminary clinical results and outcomes from later-stage trials; the occurrence of significant adverse events or other undesirable side effects; and the uncertainty surrounding regulatory approvals required for commercialization in the U.S., Europe or other international jurisdictions; Denali's ability to advance a pipeline of product candidates or develop commercially successful products; 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 its product candidates; implementation of Denali's strategic plans for its business, product candidates and blood-brain barrier platform technology; Denali's ability to obtain additional capital to finance its operations, as needed; Denali's ability to accurately forecast future financial results in the current environment; and other risks and uncertainties, including those described in Denali's most recent Annual and Quarterly Reports on Forms 10-K and 10-Q filed with the Securities and Exchange Commission (SEC) on February 27, 2025 and November 6, 2025, respectively, and Denali's future reports to be filed with the SEC. Denali's product candidates are investigational, and their safety and efficacy profiles have not yet been established. No Denali product candidates have been approved by any Health Authority for any use. 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.

Investor Contact:
Laura Hansen, Ph.D.
hansen@dnli.com

Media Contact:
Erin Patton
epatton@dnli.com

Source: Denali Therapeutics Inc.