Denali Therapeutics Announces Successful Meeting with the FDA and Plans to File for Accelerated Approval of Tividenofusp Alfa (DNL310) for the Treatment of MPS II (Hunter Syndrome)

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- Recent successful meeting with the FDA provides path to file for accelerated approval and subsequent conversion to full approval
- Plan to submit biologics license application (BLA) early in 2025 under the accelerated approval pathway
- New Phase 1/2 data will be presented this week at SSIEM 2024 demonstrating robust and durable biomarker responses and positive effects on clinical outcomes

SOUTH SAN FRANCISCO, Calif., Sept. 03, 2024 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (Nasdaq: DNLI) today announced the outcome of a recent successful meeting with the Center for Drug Evaluation and Research (CDER) division of the U.S. Food and Drug Administration (FDA) providing a path to filing a biologics license application (BLA) for accelerated approval and subsequent conversion to full approval for tividenofusp alfa (DNL310) for the treatment of MPS II (Hunter syndrome). Agreement was reached that cerebrospinal fluid heparan sulfate (CSF HS) is reasonably likely to predict clinical benefit and can be used as a surrogate endpoint to support accelerated approval for tividenofusp alfa in MPS II. Based on discussions with CDER, Denali will include preclinical and clinical data on biomarkers (CSF HS and neurofilament light (NfL)) and safety in the BLA for tividenofusp alfa as a treatment of MPS II and intends to submit the BLA under the accelerated approval pathway in early 2025.

“We thank CDER for a positive and collaborative discussion and their guidance on CSF HS as a surrogate biomarker, which we see as a significant step towards accelerating development of medicines for individuals and families living with MPS II,” said Carole Ho, MD, Chief Medical Officer of Denali. “This milestone reflects a collective effort across the patient community, academia and industry to communicate the science and advocate for faster paths to effective treatments addressing these devastating rare diseases. We are excited by the potential to deliver a new MPS treatment sooner using the accelerated approval pathway. We also look forward to plans for conversion to full approval following completion of the global Phase 2/3 COMPASS study, and we are grateful for the continued participation and commitment of patients, clinicians, and study teams involved in the tividenofusp alfa clinical studies.”

“The Phase 1/2 data show that treatment with tividenofusp alfa produces robust and durable effects, with normalization of key disease biomarkers and improvement or stabilization in associated CNS and somatic clinical endpoints,” said Barbara Burton, MD, Professor of Pediatrics, Genetics, Genomics and Metabolism at Feinberg School of Medicine in Chicago, who will present the Phase 1/2 data at the SSIEM conference. “The totality of data support Denali's plans to file for accelerated approval of tividenofusp alfa with the potential to address a critical unmet need for CNS-penetrant therapies in MPS II.”

Highlights of Phase 1/2 Data Being Presented at SSIEM 2024
Denali also announced new interim data from the Phase 1/2 study being presented at the Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM 2024) taking place September 3-6, 2024, in Porto, Portugal. The presentations include data from additional study participants (N=37) and longer duration of treatment with tividenofusp alfa (up to Week 129) as well as new analyses on biomarkers and clinical outcomes. Highlights are summarized as follows:

- **CSF HS:** 90% mean reduction in CSF HS from baseline at Week 24 with all participants having normal or near normal levels at Week 24. CSF HS reduction was sustained through Week 104.
- **Urine GAGs:** Proportion of participants with normal total urine glycosaminoglycans (GAGs) (colorimetric method) increased from 5% of participants at baseline to 77% at Week 24, and the effect was sustained through Week 129. Importantly, the majority of patients were on standard of care prior to switching to tividenofusp alfa, without a protocol defined washout period, suggesting additional urine GAG reduction with tividenofusp alfa treatment.
- **Serum NfL:** Significant and sustained reduction of serum NfL from baseline with all participants who had reached Week 129 having normal or near normal levels, suggesting a reduction of neuronal injury in participants with MPS II. More rapid NfL reductions were associated with younger age.
- **Clinical Outcomes:** Improvement or stabilization in adaptive behavior and cognitive scores, hearing, liver volume, and growth outcomes were observed.
- **Safety:** Tividenofusp alfa was generally well tolerated, with a safety profile that continues to support development as a treatment for MPS II.

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 responsible for the breakdown of the glycosaminoglycans (GAGs) heparan and dermatan sulfate in lysosomes. Symptoms often begin emerging around age two and include physical complications, including organ dysfunction, joint stiffness, hearing loss and impaired growth leading to short stature, and neurocognitive symptoms with impaired development. The disease is characterized by a buildup of 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 (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 the MPS community.

About tividenofusp alfa (DNL310)
Tividenofusp alfa (DNL310) is a fusion protein composed of IDS fused to Denali's proprietary Enzyme Transport Vehicle (ETV), which is engineered to cross the BBB via receptor-mediated transcytosis into the brain and to enable broad delivery of IDS into cells and tissues throughout the body 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 enrolling the Phase 2/3 COMPASS study in North America, South America, Europe, and Australia. The Phase 2/3 COMPASS study is expected to enroll 54 participants with MPS II with and without neuronopathic disease. The participants are randomized 2:1 to receive either tividenofusp alfa (DNL310) or idursulfase, respectively. Cohort A includes children ages 2 to 6 with neuronopathic disease; Cohort B includes children ages 6 to 26 without neuronopathic disease. More information about the COMPASS study can be found here.

About Denali's Transport Vehicle 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 Transport Vehicle (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 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 technology demonstrate more than 10- to 30-fold greater brain exposure than similar antibodies and enzymes without this technology. Oligonucleotides engineered with the TV technology 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 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 tividenofusp alfa (DNL310), including enrollment in the ongoing Phase 1/2 study and Phase 2/3 COMPASS study and the timing and availability of data from these studies, interactions with the FDA and the timing, pathway, and likelihood of regulatory approval, overall development plans, and statements made by Denali's Chief Medical Officer and Dr. Barbara Burton. 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 28, 2024, and August 1, 2024, 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.

Investor Contact

Laura Hansen, Ph.D.
Vice President, Investor Relations
(650) 452-2747
hansen@dnli.com

Media Contact
Rich Allan
FGS Global
Rich.Allan@fgsglobal.com
503-851-0807

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