Denali Therapeutics Announces U.S. FDA Approval of AVLAYAH ™ (tividenofusp alfa-eknm) for Treatment of Hunter Syndrome (MPS II)

March 25, 2026

- *First new FDA-approved treatment option in nearly 20 years for families living with this rare lysosomal storage disease*
- *First FDA-approved medicine in emerging new class of biotherapeutics that leverage transferrin receptor to cross blood-brain barrier*
- *Denali's first medicine enabled by its TransportVehicle™ platform designed to deliver biotherapeutics to whole body, including brain*
- *Rare Pediatric Disease Priority Review Voucher (PRV) awarded in connection with FDA approval*
- *Denali to host conference call and webcast today at 12:30 p.m. Eastern time*

SOUTH SAN FRANCISCO, Calif., March 25, 2026 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (Nasdaq: DNLI) today announced the U.S. Food and Drug Administration (FDA) has granted accelerated approval for AVLAYAH™ (tividenofusp alfa-eknm), the first FDA-approved biologic specifically designed to cross the blood-brain barrier and reach the whole body, including the brain. AVLAYAH is an enzyme replacement therapy indicated for the treatment of neurologic manifestations of Hunter syndrome (mucopolysaccharidosis type II, or MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

"The approval of AVLAYAH is a new era for the Hunter syndrome community as we deliver the first FDA-approved therapy designed to cross the brain's protective barrier for individuals and families living with this debilitating disease. This approval reflects the determination and partnership of the MPS community, as well as the FDA's collaborative engagement to incorporate biomarker evidence to help accelerate the development of urgently needed treatments," said Ryan Watts, Ph.D., co-founder and Chief Executive Officer of Denali Therapeutics. "This milestone validates our TransportVehicle platform and its potential to overcome the long-standing challenge of delivering biologic medicines across the blood-brain barrier, with the aim to transform the treatment of a wide range of neurodegenerative diseases, lysosomal storage disorders and other serious diseases that impact millions worldwide."

Hunter syndrome is a rare genetic 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 Hunter syndrome, GAGs build up in cells throughout the body, including the brain, resulting in progressive damage to organs and tissues beginning at a young age. Individuals living with the disease can develop cognitive, behavioral, hearing and motor decline that may include losing the ability to speak and walk.

"The FDA approval of AVLAYAH represents a breakthrough advance as the first therapeutic innovation for the Hunter syndrome community in nearly 20 years," said Joseph Muenzer, M.D., Ph.D., lead investigator of the AVLAYAH Phase 1/2 clinical trial, 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 neurologic manifestations of Hunter syndrome, which affect nearly all patients, have been one of the most challenging and persistent medical needs for the community and a central focus of many years of scientific research. As the first FDA-approved, brain-penetrant medicine for Hunter syndrome, AVLAYAH will substantially change how we treat patients and has the potential to become a new standard of care."

The approval of AVLAYAH is based on the reduction of a key disease biomarker, cerebrospinal fluid heparan sulfate (CSF HS), as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of neurologic manifestations of Hunter syndrome. In a Phase 1/2 clinical trial, AVLAYAH demonstrated a 91% (95% CI: 89%, 92%) reduction in CSF HS levels from baseline by week 24 of treatment. At week 24, 93% (41 of 44) of AVLAYAH-treated patients had CSF HS levels within the range of individuals without Hunter syndrome. The most common adverse reaction in the study was infusion-related reactions. Results from the Phase 1/2 study were published in the January 1, 2026, issue of *The New England Journal of Medicine*. The ongoing global Phase 2/3 COMPASS study is designed to generate confirmatory evidence and support global regulatory submissions for AVLAYAH. This study includes young adults living with Hunter syndrome.

"Today's accelerated approval of AVLAYAH is an important advancement for the Hunter syndrome community as the first and only enzyme replacement therapy designed to reach the central nervous system and periphery that is now FDA-approved to treat neurologic manifestations for individuals living with this disease. We extend our sincere gratitude to the study participants and families, investigators, clinicians and advocates whose courage and commitment made the approval of AVLAYAH possible," said Peter Chin, M.D., Chief Medical Officer and Head of Development of Denali Therapeutics. "We continue to study AVLAYAH in our Phase 2/3 COMPASS study with the goal of confirming the clinical evidence across the MPS II patient spectrum."

"This accelerated approval for MPS II based on a biomarker as a surrogate endpoint is an extraordinary day for the MPS and rare disease community. It represents both recognition that time matters profoundly for families affected by these devastating disorders and the potential to accelerate drug development more broadly across MPS and other rare diseases," said Terri Klein, President and Chief Executive Officer of the National MPS Society. "This approval affirms that when strong science and advocacy come

together, meaningful change, continued progress and hope are possible for individuals living with MPS and other rare diseases who are waiting for treatments."

"For families living with Hunter syndrome, progress has often felt incremental while the disease itself continues to move relentlessly forward. For many, disease progression includes cognitive impacts that can add emotional weight to an already challenging diagnosis," said Kristin McKay, President and Executive Director of Project Alive and parent of a child with Hunter syndrome. "Families have been waiting for new options that reach the brain, so the availability of this new therapeutic approach brings renewed optimism and hope for our community."

AVLAYAH is composed of the IDS enzyme fused to Denali's proprietary TransportVehicle™ (TV) platform, which binds to the transferrin receptor (TfR) and delivers IDS to peripheral tissues and to the central nervous system through receptor-mediated transcytosis across the blood-brain barrier. AVLAYAH is the first FDA-approved TfR-enabled medicine engineered to specifically cross the blood-brain barrier.

AVLAYAH is administered once weekly and will be available in the U.S. shortly after approval. Denali Therapeutics will offer personalized support services to patients, caregivers and healthcare providers through Denali Patient Services, a dedicated program offering individualized assistance with treatment access and support resources. For more information about Denali Patient Services, call 844-DNLI365 (844-365-4365).

In connection with the approval of AVLAYAH, the FDA granted Denali Therapeutics a Rare Pediatric Disease Priority Review Voucher (PRV). This voucher may be used to obtain priority review for a future marketing application or transferred to another sponsor. The PRV program is intended to incentivize the development of therapies for serious and life-threatening rare pediatric diseases by providing a mechanism to potentially accelerate regulatory review timelines for subsequent applications.

Conference Call and Webcast Information

Denali Therapeutics will host a live conference call and webcast to discuss the FDA approval of AVLAYAH beginning at 12:30 p.m. Eastern Time today. The webcast can be accessed on the Events page of the Investor section on Denali's corporate website at https://investors.denalitherapeutics.com/events or click here. The archived webcast and slides will be available on Denali's website following the event.

About the AVLAYAH Clinical Trial Program

The accelerated approval of AVLAYAH is based on a Phase 1/2 international, multi-center, open-label trial in 47 enzyme replacement therapy (ERT)-naïve (n=15) and previously treated (n=32) study participants (aged 0.3–13 [median, 5] years) with Hunter syndrome (MPS II). The primary objective of the Phase 1/2 study was to evaluate the safety and tolerability of AVLAYAH, and secondary objectives evaluated central nervous system and peripheral effects of AVLAYAH by measuring the glycosaminoglycan (GAG) heparan sulfate (HS) in cerebrospinal fluid (CSF) and urine, adaptive behavior and liver volume. Continued approval for AVLAYAH may be contingent upon verification of clinical benefit in the Phase 2/3 COMPASS confirmatory trial, in which participants are randomized 2:1 to receive either AVLAYAH or idursulfase, respectively. Denali is conducting the Phase 2/3 COMPASS study in participants with Hunter syndrome in North America, South America and Europe to support global regulatory approval. As previously announced, Cohort A of the COMPASS study has completed enrollment, and Cohort B is currently enrolling. More information about the COMPASS study can be found here.

About Hunter Syndrome (MPS II)

Hunter syndrome, also known as MPS II, is a rare genetic lysosomal storage disorder that primarily affects boys and impacts approximately 500 individuals in the United States and 2,000 individuals worldwide. The disease is caused by mutations in the iduronate 2-sulfatase (IDS) gene that 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.

About AVLAYAH™ (tividenofusp alfa-eknm)

AVLAYAH (tividenofusp alfa-eknm) is an intravenous enzyme replacement therapy composed of the iduronate 2-sulfatase (IDS) enzyme fused to Denali's proprietary TransportVehicle™ (TV) platform. The Fc component of AVLAYAH binds to the apical domain of the transferrin receptor (TfR) and delivers IDS to peripheral tissues and to the central nervous system through receptor-mediated transcytosis across the blood-brain barrier. AVLAYAH is internalized via binding to the mannose-6-phosphate receptor on the cell surface and transported into lysosomes where it is thought to exert enzymatic activity and reduce accumulated glycosaminoglycans (GAGs). In addition, since TfR is ubiquitously expressed, it is expected that the interaction of AVLAYAH and TfR will contribute to its uptake into cells in the brain and peripheral tissues. In addition to Rare Pediatric Disease Designation and Breakthrough Therapy Designation, the U.S. Food and Drug Administration granted Fast Track and Orphan Drug designations to AVLAYAH for the treatment of MPS II.

The European Medicines Agency has granted Priority Medicines designation to tividenofusp alfa. AVLAYAH is not approved by health authorities outside of the U.S.

AVLAYAH U.S. Indication

AVLAYAH is approved for the treatment of neurologic symptoms in pediatric patients weighing at least 5 kg with Hunter syndrome prior to advanced neurologic disease. This approval is based on a reduction of heparan sulfate (HS) in the cerebrospinal fluid (CSF) surrounding the brain and spinal cord. Studies are ongoing to confirm how well it works in improving clinical symptoms.

Limitations of Use

AVLAYAH is not recommended for use in combination with other enzyme replacement therapies.

Important Safety Information

AVLAYAH may cause serious side effects, including:

Hypersensitivity Reactions including Anaphylaxis. Life-threatening allergic reactions occurred both early in treatment and after many doses over time, including:

- Fast heartbeat
- Dizziness or fainting
- Wheezing
- Vomiting
- Hives
- Swelling of the lips and tongue

Notify your healthcare provider immediately if these symptoms occur. If a serious allergic reaction happens, your treatment will be stopped and emergency treatment will be given, including use of epinephrine.

Infusion-Associated Reactions (IARs). IARs occurred during or within 24 hours after receiving AVLAYAH, including:

- Chills
- Swelling
- Low blood pressure (dizziness or fainting)
- Fast heartbeat
- Hives
- Wheezing
- Fever
- Flushing or reddening of the skin
- Rash
- Cough
- Diarrhea
- Abdominal pain
- Vomiting
- Headache
- Irritability
- Small bumps on the skin

If you have an IAR, your doctor may slow down, pause, adjust your dose, or stop the infusion depending on how serious the reaction is. You may also be given medicine before infusions to help prevent these reactions. Patients with heart or lung problems may be at higher risk of serious complications from these reactions and will be monitored closely.

Anemia (Low Red Blood Cell Count) occurred during AVLAYAH treatment and may require periodic laboratory tests for hemoglobin. Contact your healthcare provider if you experience any symptoms (e.g., fatigue, pale skin) suggestive of anemia.

Membranous Nephropathy (Kidney disorder that affects the filters that help remove wastes and fluids from the kidney) occurred in an AVLAYAH-treated patient. Your doctor will monitor your kidney function during treatment.

The most common side effects (in 20% or more of patients):

- Infusion-associated reactions
- Upper respiratory infections
- Ear infection
- Fever
- Anemia (low red blood cell count)
- Cough
- Vomiting
- Diarrhea
- Rash
- COVID-19
- Runny or congested nose
- Falls
- Headache

- Skin injuries
- Hives

Contact your healthcare provider right away if you experience any side effects. These are not all the possible side effects of AVLAYAH. You may report side effects to FDA at www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to Denali Therapeutics at 1-833-ONE-DNLI (1-833-663-3654).

Please see the full Prescribing Information, including Boxed Warning, at https://www.denalitherapeutics.com/wp-content/uploads/2026/03/USPI-AVLAYAH-Mar2026.pdf for additional Important Safety Information.

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 five TV-enabled programs are currently in clinical development.

About Denali Therapeutics

Denali Therapeutics Inc. 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 is advancing toward its goal of delivering effective medicines to transform life for people with neurodegenerative diseases, lysosomal storage disorders and other serious diseases. For more information, please visit www.denalitherapeutics.com.

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 Denali's TransportVehicle™ platform, including its potential application across current and future product candidates and its ability to deliver therapeutics to the whole body, including the brain; plans and expectations related to AVLAYAH™, including its therapeutic potential, efficacy, safety profile, availability, launch timing, patient access, support services and potential side effects; expectations regarding the adequacy of the Phase 1/2 trial and the Phase 2/3 COMPASS trial results to support regulatory submissions, confirm clinical benefit and achieve approvals from the European Medicines Agency (EMA) or other global regulatory agencies; plans to conduct development and commercialization activities for AVLAYAH and other product candidates; expectations regarding Denali's Rare Pediatric Disease Priority Review Voucher (PRV), including its potential value and any strategic benefits; and statements made by Dr. Watts, Dr. Muenzer, Dr. Chin, Ms. McKay and Ms. Klein regarding the potential benefits, future clinical impact and treatment paradigm of AVLAYAH and related technologies. 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; 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 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; 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; the implementation and success 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 Form 10-K filed with the Securities and Exchange Commission (SEC) on February 26, 2026, and Denali's future reports to be filed with the SEC. Except

for AVLAYAH, Denali's product candidates are investigational, and their safety and efficacy profiles have not yet been established. 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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A video accompanying this announcement is available at https://www.globenewswire.com/NewsRoom/AttachmentNg/9bb19496-6824-41c1-a066-d8b4339712b8

Source: Denali Therapeutics Inc.