US FDA approves Denali Therapeutics' Avlayah for treatment of Hunter syndrome

Denali Therapeutics Inc., a biotechnology company, announced the US 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 paediatric 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, behavioural, 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 US 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.

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 paediatric diseases by providing a mechanism to potentially accelerate regulatory review timelines for subsequent applications.

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 behaviour 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.

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.

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 Paediatric Disease Designation and Breakthrough Therapy Designation, the US 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 US.

Avlayah is approved for the treatment of neurologic symptoms in paediatric 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.

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.

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.

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