UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported):

July 7, 2025

Denali Therapeutics Inc.

(Exact name of registrant as specified in its charter)

Delaware	001-38311	46-3872213
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

161 Oyster Point Blvd.
South San Francisco, California 94080
(Address of principal executive offices, including zip code)

(650) 866-8547
(Registrant's telephone number, including area code)

Not Applicable
(Former name or former address, if changed since last reports)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol (s)	Name of each exchange on which registered
Common Stock, par value $0.01 per share	DNLI	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On July 7, 2025, Denali Therapeutics Inc. issued a press release announcing that the U.S. Food and Drug Administration has accepted and granted Priority Review of its Biologics License Application for tividenofusp alfa for the treatment of Hunter syndrome (MPS II).

A copy of the press release is attached hereto as Exhibit 99.1 and incorporated herein by reference.

The information furnished in this Item 7.01 and Item 9.01 (including Exhibit 99.1) shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press release dated July 7, 2025.
104	Cover Page Interactive Data File (formatted as Inline XBRL)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

DENALI THERAPEUTICS INC.

Date: July 7, 2025

By: /s/ Alexander O. Schuth
Alexander O. Schuth, M.D.
Chief Operating and Financial Officer

Denali Therapeutics Announces FDA Acceptance and Priority Review of Biologics License Application (BLA) for Tividenofusp Alfa for Hunter Syndrome (MPS II)

- *FDA assigns PDUFA target action date of January 5, 2026, for decision on accelerated approval*
- *Tividenofusp alfa is designed to deliver missing enzyme to entire body and cross blood-brain barrier into the brain*
- *Tividenofusp alfa leads company's broader TransportVehicle™-enabled pipeline*

SOUTH SAN FRANCISCO, Calif., – July 7, 2025 – Denali Therapeutics Inc. (Nasdaq: DNLI) today announced that the U.S. Food and Drug Administration (FDA) has accepted for review the Biologics License Application (BLA) seeking accelerated approval for tividenofusp alfa for the treatment of Hunter syndrome (mucopolysaccharidoses type II, or MPS II), a rare and progressive genetic disorder. The FDA granted the BLA Priority Review with a Prescription Drug User Fee Act (PDUFA) target action date of January 5, 2026.

Hunter syndrome is caused by a deficiency in the iduronate 2-sulfatase (IDS) enzyme, which is needed to break down complex sugars called glycosaminoglycans that build up in the brain and body, starting at a young age. Current therapies do not cross the blood-brain barrier and lack the potential to address the impact of the disease on cognitive abilities and behavior. Tividenofusp alfa is an investigational, next-generation enzyme replacement therapy composed of IDS fused to Denali's TransportVehicle™ platform and is designed to deliver IDS into the brain and the body, aiming to treat neurological manifestations of the disease in addition to physical symptoms.

"We are grateful to the FDA for their recognition of the urgent need for new therapies that could offer a significant improvement in the treatment of Hunter syndrome, as reflected by their priority review designation for our Biologics License Application for tividenofusp alfa," said Carole Ho, M.D., Chief Medical Officer and Head of Development of Denali Therapeutics. "If FDA-approved, tividenofusp alfa would mark the first significant advancement in nearly two decades for enzyme replacement therapy for individuals living with Hunter syndrome because of its potential for delivery to tissues throughout the brain and the body. This is also a pivotal milestone for our TransportVehicle platform, which continues to progress with the aim of treating a wide range of lysosomal storage diseases and neurodegenerative disorders."

The BLA submission is supported by data from the open-label, single-arm Phase 1/2 study of tividenofusp alfa in 47 participants with Hunter syndrome. Denali continues to prepare for a potential commercial launch in the U.S. and is conducting the ongoing Phase 2/3 COMPASS study to support global regulatory approvals.

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). The U.S. Food and Drug Administration has granted Fast Track and Breakthrough Therapy designations to tividenofusp alfa for development in the treatment of MPS II. The European Medicines Agency has granted Priority Medicines designation to tividenofusp alfa.

The Phase 2/3 COMPASS study is enrolling 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, proteins, and oligonucleotides across 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 developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for the treatment of neurodegenerative diseases and lysosomal storage diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the BBB, 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 plans, timelines, and expectations related to Denali's TransportVehicle™ (TV) platform and its therapeutic and commercial potential; plans, timelines, and expectations relating to tividenofusp alfa (DNL310), including the conduct of the ongoing Phase 2/3 COMPASS study, the timing of the PDUFA action date and the likelihood of regulatory approval, and the timing and likelihood of commercial launch; expectations for ongoing communications with the FDA; the impact of any tividenofusp alfa approval on other TV-enabled programs; tividenofusp alfa's therapeutic potential; and statements made by Denali's Chief Medical 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: risks that the PDUFA action date may be extended and the FDA may ultimately determine not to approve the BLA in its present form or at all; 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 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; 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; 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 May 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.

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