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 25, 2021

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) 866-8548
(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))

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. ☐

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

Item 8.01 Other Events.

On July 25, 2021, the Company issued a press release announcing positive interim data from the Phase 1/2 study of ETV:IDS (DNL310) for the potential treatment of Hunter Syndrome that was presented at MPS 2021, the 16th Annual International Symposium of MPS and Related Diseases, which took place virtually on July 25, 2021.

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

The information furnished in this Item 8.01 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 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 25, 2021.
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 26, 2021

By: /s/ Steve E. Krognes
Steve E. Krognes
Chief Financial Officer and Treasurer

Denali Therapeutics Announces Positive Interim Data from Phase 1/2 Study with ETV:IDS (DNL310) in Patients with the Lysosomal Storage Disease Hunter Syndrome (MPS II)

- Rapid reduction and sustained normalization of heparan sulfate in CSF demonstrated robust and durable CNS activity with intravenous administration, and enhanced peripheral activity with reductions in urine and serum heparan sulfate after switching from standard-of-care idursulfase
- Global Impression of Change scales data suggested clinical improvement in overall MPS II symptoms, cognitive abilities, behavior, and physical abilities
- Exploratory biomarker data demonstrated reductions in CSF lysosomal lipid biomarkers that are consistent with improved lysosomal function; and high variability in exploratory biomarker Nf-L was observed pre- and post-treatment
- Safety profile with up to 43 weeks of dosing was consistent with standard of care enzyme replacement therapy with infusion-related reactions being the most frequently observed adverse events
- Based on these data, Denali is accelerating efforts to initiate a pivotal Phase 2/3 study in 1H 2022
- Management will host a webinar for analysts and investors at 11:30 a.m. Eastern Time today

SOUTH SAN FRANCISCO, Calif., July 25, 2021 — Denali Therapeutics Inc. (NASDAQ: DNLI), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for neurodegenerative diseases, today announced additional positive interim data from a Phase 1/2 study evaluating ETV:IDS (DNL310), an investigational brain-penetrant enzyme replacement therapy intended to treat both central nervous system (CNS) and peripheral manifestations of Hunter syndrome (MPS II). The interim results being presented today at MPS 2021, the 16th International Symposium on MPS and Related Diseases, include safety data up to Weeks 43 and 25 from Cohorts A and B, respectively, 6-month biomarker data from Cohort A and up to 3-month biomarker data from Cohort B. Denali Management will host a webinar today for analysts and investors beginning at approximately 11:30 a.m. Eastern Time.

“The longer-term safety data and 6-month biomarker data on DNL310 from Cohort A continue to demonstrate durability of effect with CNS impact, improved peripheral activity after switching from standard of care, and a safety profile consistent with standard of care enzyme replacement therapy,” said Carole Ho, M.D., Denali’s Chief Medical Officer. “We are also encouraged by initial indications of improved clinical symptoms and function reported by investigators and parents in all five patients enrolled in Cohort A. In addition, this is the first time we are sharing data from Cohort B, which is designed to inform dose selection, and exploratory biomarker data demonstrate activity of DNL310 across all dose regimens. Based on these data, we are accelerating our efforts to initiate a pivotal Phase 2/3 study of DNL310 in the first half of 2022 and to begin enrolling Cohort C in the Phase 1/2 study to further investigate clinical endpoints.”

This interim analysis of the Phase 1/2 study included data on five patients enrolled in Cohort A and 12 patients enrolled in Cohort B. All patients have neuronopathic MPS II disease except for one patient with non-neuronopathic MPS II disease in Cohort B. The median age of patients is 6 years in both cohorts, with the youngest patients aged 5 and 2 in Cohorts A and B, respectively. All patients received weekly intravenous doses of DNL310 after switching from idursulfase enzyme replacement therapy on Day 1 of the study. Data being presented include safety data up to Weeks 43 and 25 from Cohorts A and B, respectively; 6-month and up to 3-month biomarker data from Cohorts A and B, respectively; and exploratory clinical Global Impression of Change data from Cohort A up to Week 24.

Results across Cohorts A and B showed that, following the switch from idursulfase to DNL310, the levels of heparan sulfate in cerebrospinal fluid (CSF) normalized in all patients analyzed (n=15), with rapid response observed in most patients (n=12) by Week 7, which is consistent with crossing of the BBB by DNL310 and activity in tissues of the CNS. Rapid normalization of CSF heparan sulfate at low dose regimens suggest that BBB crossing with Denali's Transport Vehicle (TV) was robust and efficient. Furthermore, the observed decline in urine and serum heparan sulfate was consistent with improved peripheral activity with DNL310.

Exploratory clinical data suggest improved clinical symptoms and function for all five patients enrolled in Cohort A as reported by investigators and parents. Based on Global Impression of Change scales [Clinician Global Impression of Change (CGI-C) and Parent Global Impression of Change (PGI-C)], which are standardized assessment scales used to measure change, the data showed clinical improvement in overall MPS II symptoms, cognitive abilities, behavior, and physical abilities.

Exploratory lysosomal lipid data showed reductions, which are consistent with improved lysosomal function: 10 of 15 patients across Cohorts A and B had normal GM3 ganglioside levels, including patients on low dose regimens and with shorter duration of treatment. In addition, reductions in levels of bis(monoacyl glycerol)-phosphate (BMP) and a potential reduction in levels of glucosylceramide (GlcCer) were observed in Cohort A at Week 24.

High within patient variability in levels of neurofilament (Nf-L), an exploratory biomarker of neuronal structure, was observed pre- and post-treatment. Data from an ongoing observational natural history study conducted by Denali showed a marked increase in mean levels of serum Nf-L over a 4.5- to 6-month period in patients (n=3) who subsequently enrolled in Cohort A of the Phase 1/2 study. During the 6-month treatment period of the Phase 1/2 study, mean levels of serum and CSF Nf-L in Cohort A (n=5) showed a modest increase. Denali believes that the utility of Nf-L as a treatment response biomarker in MPS II will require further investigation.

The safety profile of DNL310 remained consistent with standard of care enzyme replacement therapy. DNL310 was generally well tolerated with the most common treatment-emergent adverse events being infusion-related reactions (IRRs). IRRs occurred in 12 of 17 (71%) patients: the majority had mild (n=5) or moderate (n=6) IRRs, and 1 patient had severe IRRs. A total of 3 serious adverse events (SAEs) were reported: 1 previously reported SAE for a patient enrolled in Cohort A based on a mild IRR, and 2 SAEs in a patient enrolled in Cohort B based on severe IRRs. The SAEs resolved, and both patients are continuing in the study. All other treatment-emergent adverse events were mild or moderate.

The study continues without modification following recommendation by an independent data monitoring committee on July 9, 2021.

"DNL310 is our lead program enabled by our blood-brain barrier Transport Vehicle platform, and these data continue to validate the platform's potential as we advance additional TV-enabled programs toward the clinic," said Ryan Watts, Ph.D., Denali's Chief Executive Officer. "Our DNL310 program exemplifies application of Denali's core scientific principles to increase likelihood of success by targeting degenogenes, engineering therapeutics to cross the blood-brain barrier, and using biomarkers to inform development. We are encouraged by these interim data and we look forward to continued collaboration with the community to advance MPS II research and DNL310 as a potential treatment for affected individuals and their families."

Families interested in learning more about Denali's efforts related to the discovery and development of therapeutics for the potential treatment of Hunter syndrome are invited to visit EngageHunter.com, the Denali Hunter syndrome community engagement website.

Denali Webinar for Analysts and Investors

Denali will host a webinar for analysts and investors to present the interim data from the Phase 1/2 study of DNL310. The webinar will begin at approximately 11:30 a.m. EDT / 8:30 a.m. PDT on Sunday, July 25, 2021, and will be available on Denali's corporate website on the Events page under the Investor section and can be accessed by following this link. An archived replay of the webinar will be available for at least 30 days following the event.

About DNL310 and Hunter Syndrome (MPS II)
Hunter syndrome (MPS II) is a rare neurodegenerative lysosomal storage disease caused by mutations in the gene that encodes for the enzyme iduronate-2-sulfatase (IDS). The resultant reduction or loss of IDS enzyme activity leads to accumulation of glycosaminoglycans, which causes lysosomal dysfunction and neurodegeneration as well as progressive damage to multiple organs including bone, cartilage, heart and lung. Current standard of care enzyme replacement treatment does not address neuronopathic manifestations of the disease as it does not sufficiently cross the blood-brain barrier (BBB). DNL310 is an investigational 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. More information about the ongoing Phase 1/2 study of DNL310 in patients with Hunter syndrome can be found on ClinicalTrials.gov by following this link.

About Denali's TV Platform
The 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 CNS diseases by preventing most drugs from reaching the brain in therapeutically relevant concentrations. Denali's 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 fragments that bind to specific natural transport receptors, such as transferrin receptor, which are expressed at the BBB and deliver TV and its therapeutic cargo to the brain through receptor-mediated transcytosis. In animal models, antibodies and enzymes engineered to the TV technology demonstrate more than 10- to 30-fold greater brain exposure than similar antibodies and enzymes 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. ETV:IDS (DNL310) is Denali's lead TV-enabled program in Phase 1/2 development for the potential treatment of Hunter syndrome (MPS II).

About the EngageHunter.com Website
EngageHunter.com — the Denali Hunter syndrome (MPS II) community engagement website — is an online destination for emerging information on Denali's scientific advances in Hunter syndrome research and Denali's clinical trials. Visitors who register on the Engage Hunter website will receive updates on Denali's research and future Denali investigational studies.

About Denali Therapeutics
Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for neurodegenerative 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 Denali's plans, timelines and expectations related to DNL310, the DNL310 ongoing Phase 1/2 study and expectations regarding enrollment in Cohort C, plans to accelerate efforts to initiate the planned Phase 2/3 in the first half of 2022, plans regarding other planned future studies, expectations regarding Denali's TV technology platform, the therapeutic potential of DNL310 and Denali's TV platform, and statements made by Denali's Chief Medical Officer and Chief Executive Officer. 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 early stages of clinical drug development; Denali's and its partners' ability to complete the development and, if approved, commercialization of DNL310; Denali's and its partners' ability to enroll patients in its ongoing and future clinical trials; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; the potential for clinical trial results of DNL310 to differ from preclinical, preliminary or expected results, the risk that Denali will be able to continue dose escalation in the Phase 1/2 study, whether DNL310 will cause any serious adverse events, whether DNL310 will impact downstream biomarkers of neurodegeneration, the risk that results from early clinical biomarker studies will not translate to clinical benefit in late clinical studies; and that DNL310 may not receive regulatory approval as a treatment of Hunter syndrome necessary to be commercialized. 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 26, 2021, and May 5, 2021, 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.

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