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):
February 12, 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 February 12, 2021, the Company issued a press release announcing positive three-month data from Phase 1/2 Study with ETV:IDS (DNL310) in Patients with 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 8.01 and Item 9.01 (including Exhibits 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 February 12, 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: February 12, 2021

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

Denali Therapeutics Reports Positive Three-Month Data from Phase 1/2 Study with ETV:IDS (DNL310) in Patients with Hunter Syndrome (MPS II)

- **Sustained normalization and further decreased levels of CSF glycosaminoglycan heparan sulfate, a key CNS disease biomarker, observed after three months of intravenous dosing**
- **Reductions in exploratory CSF biomarkers consistent with improved lysosomal function**
- **Reductions in levels of urine glycosaminoglycans following a switch from idursulfase support potential for improved peripheral effects relative to standard of care**
- **Generally well tolerated with safety profile consistent with other enzyme replacement therapies; most frequently observed adverse events of mild or moderate infusion-related reactions**
- **Management will host a webinar for analysts at 8:00 a.m. Eastern Time today**

SOUTH SAN FRANCISCO – February 12, 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 results from the ongoing Phase 1/2 study evaluating ETV:IDS (DNL310) as a potential brain-penetrant enzyme replacement therapy for treating both central nervous system (CNS) and peripheral manifestations of Hunter syndrome (MPS II). The data will be presented later today during a late-breaker session at WORLD*Symposium*™. Denali management will host an analyst webinar today beginning at 8:00 a.m. Eastern Time to discuss both interim clinical and new preclinical data that will be presented at the conference.

An interim analysis included data on a total of five patients enrolled in Cohort A in the Phase 1/2 study, who all received three months of weekly intravenous doses of DNL310 after switching from idursulfase enzyme replacement therapy on Day 1 of the study. Key results included:

- Normal levels of heparan sulfate, a glycosaminoglycan (GAG), in cerebrospinal fluid (CSF) that were seen after four weeks of dosing in four of five patients were sustained after three months of dosing (mean 85% reduction across Cohort A; $p<0.001$); heparan sulfate levels were further significantly reduced and approached normal levels in the fifth patient (from 25% to 73% reduction from one to three months, respectively).
- Reductions in downstream exploratory CSF biomarkers, GM3 and BMP (lysosomal lipids), of 39% and 15%, respectively, were observed after eight weeks of dosing with DNL310, consistent with improvement in lysosomal function.
- Reductions in urine heparan sulfate and dermatan sulfate following a switch from idursulfase, of 76% and 82%, respectively, were observed after eight weeks of dosing of DNL310, supporting potential for improved peripheral effects relative to standard of care.
- DNL310 was generally well tolerated with no dose reductions and all five patients continue in the study. The most frequently observed adverse events were mild or moderate infusion-related reactions in three of five patients, which is consistent with other enzyme replacement therapies (ERTs).
- Based on three-month clinical data, doses of DNL310 from 3 mg/kg to 30 mg/kg are generally well tolerated and provide flexibility for dose selection in clinical studies.

“We are encouraged by these new Phase 1/2 data, which continue to support the overall safety profile and biomarker effects of DNL310 as an investigational treatment in Hunter syndrome,” said Carole Ho, M.D., Denali’s Chief Medical Officer. “Importantly, at dose levels resulting in robust and durable biomarker response, DNL310 appears generally well tolerated and consistent with standard of care ERT. We are pleased to observe that early biomarker effects initially seen after four weeks of treatment with DNL310 were sustained after three months of dosing. We are also encouraged by the findings related to exploratory lipid biomarkers which indicate, for the first time, improvement in lysosomal function. Taken together, these data support our previously announced decision to expand and advance clinical studies with DNL310 as a potential treatment for both body and brain in patients with Hunter syndrome.”

Denali also presented preclinical research at WORLD*Symposium*™ on a mouse model of Hunter syndrome showing that ETV:IDS treatment reduces CSF GAGs and that these reductions are correlated with GAG reductions in the brain. Furthermore, reduction in CSF GAG levels was associated with subsequent improvements in lysosomal function, neurodegeneration biomarkers, neurobehavioral outcomes and correction of skeletal disease manifestations in the mouse model.

“The magnitude and durability of biomarker response and tolerability seen with DNL310 provide strong support for the potential application of our Transport Vehicle (TV) technology to deliver enzymes and other therapeutic modalities to the brain,” said Ryan Watts, Ph.D., Denali’s Chief Executive Officer. “Compared to other investigational BBB transport technologies, we have engineered specific molecular properties into our TV technology for better brain uptake and biodistribution of the therapeutic cargo to relevant cell types. The DNL310 Phase 1/2 results also support the potential for systemic administration of TV-enabled therapeutics to address peripheral disease. Taken together, these data increase our confidence that DNL310 may ultimately prove to be an impactful therapy for Hunter syndrome patients and their families and that we can apply our TV technology more broadly to defeat degeneration and address other diseases with brain manifestations.”

About the DNL310 Development Program for the Potential Treatment of Hunter syndrome (MPS II)

Hunter syndrome (MPS II) is a rare neurodegenerative lysosomal storage disorder caused by a mutation 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 GAGs, 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 BBB. 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. Denali previously announced human biomarker proof-of-concept for its TV technology from Cohort A (n=5) of an ongoing Phase 1/2 study of DNL310 in patients with Hunter syndrome. The study is currently enrolling Cohort B, and a Cohort C is planned to further explore clinical endpoints. DNL310 is an investigational drug and is not approved by any health authority.

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 are delivered to the brain through receptor-mediated transcytosis. Denali research has shown that in animal models, antibodies and enzymes engineered with the TV technology have demonstrated 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).

Webinar Information

Denali will host a webinar today, Friday, February 12, at 8:00 a.m. Eastern Time to discuss the DNL310 Phase 1/2 data. A registration link will be available on the Events page under the Investor section of Denali's website at https://www.denalitherapeutics.com/investors/events or by clicking here. An archived replay of the webinar will be available for at least 30 days following the event.

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 progress and business plans; plans, timelines and expectations related to DNL310, the DNL310 development program, Denali's TV technology platform, other programs enabled by Denali's TV platform, and the ongoing Phase 1/2 study, and planned future studies, of DNL310; 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: any and all risks to Denali's business and operations caused directly or indirectly by the evolving COVID-19 pandemic; risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's agreements with its partners; Denali's early stages of clinical drug development; Denali's and its partners' ability to complete the development and, if approved, commercialization of its product candidates; 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; Denali's dependence on successful development of its blood-brain barrier platform technology and TV-enabled product candidates; Denali's and its partners' ability to conduct or complete clinical trials on expected timelines; 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, and that DNL310 may not receive regulatory approval as a treatment of Hunter syndrome necessary to be commercialized; risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's agreements with its partners; Denali's ability to continue to create a pipeline of product candidates or develop commercially successful products; 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; and other risks. 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 27, 2020, and November 5, 2020, 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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