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):

November 10, 2020

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 November 10, 2020, Denali issued a press release announcing first human biomarker proof of concept for its Transport Vehicle (TV) Technology achieved in a Phase 1/2 study of ETV:IDS (DNL310) in Hunter Syndrome (MPS II). A copy of the press release is attached hereto as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release dated November 10, 2020.
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: November 10, 2020

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

Denali Therapeutics Announces First Human Biomarker Proof of Concept for Its Transport Vehicle (TV) Technology Achieved in Phase 1/2 Study of ETV:IDS (DNL310) in Hunter Syndrome (MPS II)

- After four weekly intravenous doses of DNL310, a 76% mean reduction in CSF GAG levels (heparan sulfate) from baseline was observed, with normal healthy levels being achieved in four of five patients
- Based on Cohort A safety data review, an independent data monitoring committee recommended continuing the study without modifications, enabling progression to Cohort B, including enrollment of younger patients, and continuation of dose escalation in Cohort A
- Data provide first biomarker proof of concept in humans for Denali's proprietary TV technology designed to deliver biotherapeutics to the brain
- Management will host a webinar at 8:30 a.m. ET today

SOUTH SAN FRANCISCO – November 10, 2020 – 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 biomarker proof of concept was achieved for its Transport Vehicle (TV) technology in a Phase 1/2 study of ETV:IDS (DNL310) for the potential treatment of Hunter syndrome (MPS II). 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.

Hunter syndrome 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 glycosaminoglycans (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 (ERT) does not address neuronopathic manifestations of the disease as it does not sufficiently cross the BBB.

"The robust reduction in cerebrospinal fluid (CSF) GAG levels observed after only four weeks of treatment with DNL310 in the Phase 1/2 study exceeded our initial goal in both magnitude and timing of heparan sulfate reduction after treatment," said Carole Ho, M.D., Denali's Chief Medical Officer. "These results are encouraging because, in preclinical models of Hunter syndrome treated with intravenous DNL310, a 50% reduction in CSF GAGs is associated with protective downstream effects on lysosome function, neuronal health and improvement in neurobehavioral deficits. Our next steps are to continue dose escalation in the Phase 1/2 study and evaluate the effects of DNL310 on additional downstream biomarkers of neurodegeneration. We are most grateful to the Hunter syndrome families and clinical investigators who are participating in the Phase 1/2 study."

"A long-standing challenge in developing biotherapeutics to treat neurodegenerative diseases is the ability to transport large molecules across the blood-brain barrier safely and at therapeutic levels," said Ryan Watts, Ph.D., Denali's Chief Executive Officer. "These Phase 1/2 data are an important step towards addressing this challenge as they provide the first human biomarker validation of our proprietary TV technology platform for delivering biotherapeutics to the brain. We see significant potential to enhance or enable the delivery of enzymes, antibodies, proteins and antisense oligonucleotides to the brain using our TV platform. Now with human proof of concept achieved, we will apply additional resources to move our promising TV-enabled discovery programs forward."

The Phase 1/2 Study 4-Week Safety and Biomarker Results

The Phase 1/2 study of DNL310 is a multicenter, multiregional, open-label study to assess the safety, pharmacokinetics, and pharmacodynamics of increasing dose levels of DNL310 administered once weekly by intravenous infusion. The study has two staggered cohorts: the first (Cohort A) enrolled a total of five patients with neuronopathic MPS II aged five to ten years; the second (Cohort B) will enroll either neuronopathic or non-neuronopathic MPS II patients aged two to 18 years.

All five patients were previously on idursulfase ERT and were switched to DNL310 on Day 1 of the study. DNL310 is administered once weekly by intravenous infusion starting with a dose level of 3 mg/kg. In Cohort A, after two doses at 3 mg/kg, based on safety and tolerability, intrapatient dose escalation proceeded per the study protocol.

Key findings in five patients enrolled in Cohort A who received four weekly intravenous doses of DNL310 are summarized below:

- An independent data monitoring committee (DMC) reviewed the safety data from Cohort A and made a recommendation to continue the study and open Cohort B without protocol modifications, enabling progression to Cohort B, including enrollment of younger patients, and continuation of dose escalation in Cohort A.

- Total urine GAG levels were maintained within the same range observed in patients prior to switching from idursulfase ERT to DNL310.

- A mean reduction from baseline of 76% (p-value <0.001) was observed in CSF levels of heparan sulfate, a GAG that accumulates in MPS disorders with CNS involvement. In addition, four of five patients achieved normal healthy levels of heparan sulfate; individual percent reductions from baseline of 93%, 91%, 90%, 81%, and 25% were observed.

- A mean reduction from baseline of 53% (p-value< 0.001) was observed in CSF levels of dermatan sulfate, a GAG that is a biomarker of IDS enzyme activity that is elevated in MPS diseases both with and without neurocognitive effects; individual percent reductions from baseline were 64%, 64%, 53%, 41% and 39%.
- All five patients enrolled in Cohort A continue in the dose-escalation portion of the Phase 1/2 study.

About DNL310 for Hunter syndrome (MPS II)

DNL310 is a fusion protein composed of the lysosomal enzyme, IDS, fused to Denali's proprietary Enzyme Transport Vehicle (ETV), which is engineered to cross the blood-brain barrier by binding to transferrin receptor. Intravenous administration of ETV:IDS is designed to take advantage of a highly vascularized central nervous system (CNS), and the nearly 400 miles of capillaries in the human brain, to actively transport biotherapeutics through receptor-mediated transcytosis into the brain. Denali has engineered aspects of its TV technology for accessing all brain regions and brain cell types to enable and enhance therapeutic benefit. DNL310, Denali's lead investigational ETV:IDS, is designed to treat both the systemic and CNS manifestations of Hunter syndrome through the intravenous route of administration.

Previously, Denali published research showing for the first time that in people with Hunter syndrome, abnormalities in GAGs, the substrate of IDS enzymatic activity, are correlated with biomarkers of secondary lysosomal dysfunction (gangliosides, BMP, GluCer), axonal injury (Nf-L), and inflammation.[1]

In addition, biomarker data from multiple studies of a mouse model of Hunter syndrome demonstrate that intravenously administered ETV:IDS (1) achieved high concentration and broad distribution of IDS enzymes in the brain; (2) led to reduction in GAGs; (3) corrected the abnormal accumulation of lysosomal lipids (gangliosides, BMP, GluCer); (4) slowed neuroaxonal injury, as evidenced by a reduction in Nf-L; (5) improved neurobehavioral deficits (spatial learning and memory deficits) and motor function (locomotor performance and agility); and (6) corrected skeletal disease manifestations (trabecular and cortical bone mass in the femur).

In the mouse model of Hunter syndrome, GAG reduction in the CSF correlated with GAG reduction in the brain after systemic administration of ETV:IDS. Furthermore, an approximate 50% reduction in CSF GAG levels was associated with subsequent improvements in lysosomal function, neurodegeneration biomarkers and neurobehavioral outcomes.

The ongoing Phase 1/2 study is designed to establish safety and inform dose selection to evaluate the effects of treatment with DNL310 on neurocognitive outcomes in a subsequent planned Phase 2/3 pivotal study. Additional biomarkers of lysosomal function and neuroaxonal injury (Nf-L) will be measured in the ongoing Phase 1/2 study. Denali expects additional safety and biomarker data to be available in the first quarter of 2021 and in mid-2021.

About Denali's Transport Vehicle 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 CNS diseases by preventing most drugs from reaching the brain in therapeutically relevant concentrations.

Denali's Transport Vehicle (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. The most advanced program based on the TV technology is ETV:IDS (DNL310) for Hunter syndrome, currently in a Phase 1/2 study.

Webinar Information

Denali will host a webinar today, Tuesday, November 10, at 8:30 a.m. Eastern Time to discuss the ETV:IDS (DNL310) program. Advance registration for this webinar can be accessed using this link. The live webinar can be accessed on the Events page of the Investor Relations section of Denali's website at https://www.denalitherapeutics.com/investors/events. A replay of the webinar will be available on Denali's website for up to 30 days.

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 and 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.

Reference:

1. **Bhalla A, et al. Characterization of Fluid Biomarkers Reveals Lysosome Dysfunction and Neurodegeneration in Neuronopathic MPS II Patients. *Int J Mol Sci.* 2020 Jul 22;21(15):5188. doi: 10.3390/ijms21155188.**

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