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 10, 2022

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 10, 2022, the Company issued a press release announcing continued progress in the DNL310 (ETV:IDS) program for MPS II (Hunter Syndrome) supporting planned initiation of a Phase 2/3 clinical trial.

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 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 February 10, 2022.
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 10, 2022

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

Denali Therapeutics Announces Continued Progress in DNL310 (ETV:IDS) Program for MPS II (Hunter Syndrome) Supporting Planned Initiation of Phase 2/3 Clinical Trial

- Longer-term data in 20 patients show sustained normalization to healthy levels of CSF heparan sulfate and improvements in markers of lysosomal function consistent with durable CNS activity, now with up to one year of intravenous dosing with DNL310
- Safety profile with up to 56 weeks of dosing remains consistent with standard-of-care enzyme replacement therapy
- Data continue to support initiation of dosing with DNL310 in a potentially registrational Phase 2/3 clinical trial expected to begin in 1H 2022
- These longer-term data with DNL310 continue to provide biomarker proof of concept for Denali's Transport Vehicle (TV) platform to deliver biotherapeutics across the blood-brain barrier

SOUTH SAN FRANCISCO, Calif., Feb. 10, 2022 -- 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 that new longer-term data from an ongoing Phase 1/2 clinical trial of DNL310 (ETV:IDS) are being presented today at WORLD*Symposium*™. DNL310 is an investigational brain-penetrant enzyme replacement therapy intended to treat both central nervous system (CNS) and peripheral manifestations of MPS II (Hunter syndrome).

"The longer-term Phase 1/2 data, now up to approximately one year for Cohort A and six months for Cohort B, support DNL310 as a differentiated enzyme replacement therapy that rapidly normalizes CSF heparan sulfate and maintains improvement in CSF biomarkers of lysosomal function with weekly intravenous dosing," said Carole Ho, M.D., Denali's Chief Medical Officer. "With additional patient data now available, we are also encouraged that we continue to see improvements in exploratory clinical outcomes in the majority of individuals as assessed after six months of open label DNL310 treatment. These data continue to support initiation of a potentially registrational Phase 2/3 study of DNL310 in the first half of 2022. We look forward to continued collaboration with the MPS II community to advance research and DNL310 as a potential treatment for affected individuals and their families."

Phase 1/2 study data being presented at WORLD*Symposium*™ today at 8 a.m. Pacific Time

The Phase 1/2 study data being presented at WORLD*Symposium*™ today include longer-term biomarker data up to Weeks 49 and 24 from Cohort A and B, respectively; clinical outcomes data across Cohorts A and B at Week 24; and safety data up to Weeks 56 and 39 from Cohorts A and B, respectively. 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 on Day 1 of the study after switching from idursulfase enzyme replacement therapy. The main differences between the cohorts include exploration of different dose levels and age groups, with younger patients eligible for Cohort B.

A PDF copy of the Phase 1/2 data presentation will be available on the Investor Events section of Denali's corporate website after 8 a.m. Pacific Time.

Longer-term data demonstrate durability of CSF biomarker responses, now up to one year of dosing

Across Cohorts A (n=5) and B (n=15), all patients had normalized levels of heparan sulfate in cerebrospinal fluid (CSF) by Week 24 of treatment with DNL310, which were sustained in all 5 patients from Cohort A at Week 49. Rapid response was observed in most patients after 4 to 6 weekly intravenous doses of DNL310, including in patients on lower dose regimens of DNL310. These results are consistent with robust and efficient crossing of the BBB by DNL310 and durable activity in the CNS. Furthermore, the observed decline in urine heparan and dermatan sulfate, as well as CSF dermatan sulfate, was consistent with increased peripheral and central activity with DNL310 compared to standard-of-care, respectively.

Exploratory CSF lysosomal lipid biomarker data showed further reductions with longer duration of treatment with DNL310, consistent with improved lysosomal function. Across Cohorts A and B, CSF GM3 ganglioside levels decreased from baseline, with normalized CSF GM3 ganglioside levels apparent in all 5 patients in Cohort A at Week 49, and in 9 of 12 patients in Cohort B at Week 24 (3 of 15 total patients in Cohort B had not reached Week 24 at the time of the data cut in September 2021). In addition, available preliminary exploratory data on other biomarkers of lysosomal function demonstrated reductions in levels of glucosylceramide (GlcCer) across Cohorts A and B at Week 24 and reductions in levels of other lysosomal lipid biomarkers including bis(monoacycerol)-phosphate (BMP), GM2 and glucosylsphingosine in Cohort A at 24 weeks.

Exploratory open-label clinical outcomes data, now including Cohort B, suggest improvements in the majority of patients

Exploratory clinical outcomes data at Week 24 from Cohort A (n=5), and now including Cohort B (n=12; 3 of 15 total patients had not reached Week 24 at the time of the data cut in September 2021), suggest improved clinical symptoms and function in the majority of patients as reported by investigators and parents/caregivers. Based on Global Impression of Change scales [Clinician Global Impression of Change (CGI-C) and Parent/Caregiver Global Impression of Change (PGI-C)], which are standardized assessment scales used to measure change and modified to measure specific domains impacted by MPSII, the data showed clinical improvement in overall MPS II symptoms, cognitive abilities, and behavior from baseline.

Safety profile of DNL310, now with over one year of dosing, remains consistent with standard-of-care

The safety profile of DNL310, which now includes data up to Weeks 56 and 39 from Cohorts A and B, respectively, remains 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 15 of 20 (75%) patients: the majority had mild (n=6) or moderate (n=8) IRRs, and 1 patient had severe IRRs. Most IRRs occurred during the first 12 study weeks; IRR frequency decreased with chronic dosing, including in patients who dose escalated up to 30 mg/kg. A total of 4 serious adverse events (SAEs) were reported: 1 previously reported SAE for a patient enrolled in Cohort A based on a mild IRR; 2 previously reported SAEs in a patient enrolled in Cohort B based on severe IRRs; and 1 SAE in a patient in Cohort B hospitalized for constipation. The SAEs resolved, and all three patients are continuing in the study. There were no notable abnormalities or trends in safety laboratory evaluations except for previously reported mild or moderate anemia in 4 of 20 patients. Anemia stabilized (n=2) or resolved (n=2) while continuing treatment with DNL310. All other treatment-emergent adverse events were mild or moderate.

The study continues without modification following recommendation by an independent data monitoring committee in October 2021.

Data continue to support initiation of a potentially registrational Phase 2/3 clinical trial of DNL310

Based on the strength of the clinical and preclinical data to date, Denali plans to initiate a potentially registrational Phase 2/3 trial with DNL310 with the goal of demonstrating efficacy and safety in participants with neuronopathic and non-neuronopathic MPS II. The trial is designed to enroll two cohorts of male and female participants with a confirmed diagnosis of MPS II. Cohort A will enroll neuronopathic participants ages 2 to 6 years and Cohort B will enroll non-neuronopathic participants ages 6 to 17 years. Eligible participants are required to have been receiving maintenance enzyme replacement therapy and to have tolerated a minimum of 4 months of idursulfase therapy during the period immediately prior to screening. Participants will be randomized 2 to 1 to receive DNL310 or standard of care (idursulfase), respectively. The treatment periods are 96 weeks and 48 weeks for Cohorts A and B, respectively, followed by open label extension on DNL310. Key efficacy endpoints include: the effect of DNL310 on CSF biomarkers (CSF GAGs); the effect of DNL310 on neurobehavioral parameters; the effect of DNL310 on systemic manifestations of disease; and patient/caregiver reported outcomes. Dosing is expected to begin in the Phase 2/3 trial in the first half of 2022.

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.

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 only partially improves the peripheral manifestations of MPS II and 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 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 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.

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 and the DNL310 ongoing Phase 1/2 study, plans regarding the timing and structure of, and expectations regarding enrollment in, the Phase 2/3 study, including its initiation in the first half of 2022 and the expectation that it is potentially a registrational trial, 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. 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 ability to complete the development and, if approved, commercialization of DNL310 on expected timelines; Denali's ability to initiate and enroll patients in the Phase 2/3 study of DNL310 and other 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, early clinical, preliminary or expected results; Denali's ability to continue dose escalation in the Phase 1/2 study of DNL310; the risk of significant adverse events, toxicities or other undesirable side effects related to DNL310; 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; the risk that DNL310 may not receive regulatory approval as a treatment of Hunter syndrome necessary to be commercialized; 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 DNL310; implementation of Denali's strategic plans for its business, product candidates and blood-brain barrier platform technology, including DNL310; and other risks and uncertainties. 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 November 4, 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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