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):

January 8, 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 5.02 Departure of Directors or Principal Officers; Election of Directors; Appointment of Principal Officers.

On January 8, 2021, Nancy Thornberry was appointed to the Board of Directors (the "Board") of Denali Therapeutics Inc. (the "Company"). Ms. Thornberry will serve as a Class I director, with a term expiring at the Company's 2021 annual meeting of the stockholders.

In accordance with the Company's outside director compensation policy (the "policy"), Ms. Thornberry will receive annual cash compensation of $40,000 for her services as a member of the Board, payable quarterly in arrears on a pro-rata basis, and on January 8, 2020, Ms. Thornberry was automatically granted an initial award of a nonstatutory stock option to purchase shares of the Company's common stock and an initial award RSU together having an aggregate company-assessed value of approximately $600,000. 60% of the value of the initial awards is in nonstatutory stock options (the "Initial Option"), while the remaining 40% is in RSUs (the "Initial RSU"). For purposes of the policy, the Company values RSUs as 1 RSU for every 2 shares subject to an option. The Initial Option vests as to 25% of the shares on the one year anniversary of the grant date and as to 1/48th of the shares on each monthly anniversary of the grant date thereafter, provided that she remains a non-employee director through the applicable vesting date. The Initial RSU award vests over a four-year period, with 1/4th of the shares vesting on each anniversary of the grant date (or, for the last tranche that otherwise would vest on the fourth anniversary of the grant date, on such anniversary or, if earlier, on the day prior to the Company's next annual meeting of stockholders occurring after the third anniversary of the grant date), provided that she remains a non-employee director through the applicable vesting date. Initial awards to Ms. Thornberry were granted under and subject to terms of the Company's 2017 Equity Incentive Plan.

Ms. Thornberry will be eligible for equity awards on the same terms as other continuing non-employee members of the Board. Currently, the policy provides that on the date of each annual meeting of stockholders, each non-employee director who has been a director for six months or more on the date of the annual meeting will automatically be granted a nonstatutory stock option to purchase shares of the Company's common stock and an initial award RSU together having an aggregate company-assessed value of approximately $350,000. 60% of the value of the initial awards will be in nonstatutory stock options (the "Annual Option"), while the remaining 40% will be in RSUs (the "Annual RSU"). Each Annual Option and Annual RSU will vest fully on the earlier of the one year anniversary of the grant date or the day prior to the next annual meeting of stockholders held after the grant date, in each case provided that such director remains a non-employee director through the applicable vesting date.

Ms. Thornberry also executed the Company's standard form of indemnification agreement, a copy of which has been filed as Exhibit 10.1 to the Company's Amendment No. 2 to the Registration Statement on Form S-1 (File No. 333-221522) filed with the Securities and Exchange Commission on December 7, 2017.

There is no arrangement or understanding between Ms. Thornberry and any other persons pursuant to which Ms. Thornberry was elected as a director. In addition, Ms. Thornberry is not a party to any transaction, or series of transactions, required to be disclosed pursuant to Item 404(a) of Regulation S-K.

On January 11, 2021, the Company issued a press release announcing Ms. Thornberry's appointment as a director. The press release is attached hereto as Exhibit 99.1.

Item 7.01 Regulation FD Disclosure.

On January 8, 2021, the Company issued a press release announcing an update on its programs and expected milestones for 2021 and the Company's participation in the JP Morgan Healthcare Conference.

A copy of the press release is attached hereto as Exhibit 99.2 and incorporated herein by reference.

The information furnished in this Item 7.01 and Item 9.01 (including Exhibits 99.1 and 99.2) 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 January 11, 2021.
99.2	Press Release dated January 8, 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: January 11, 2021

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

Denali Therapeutics Announces Appointment of Nancy Thornberry to Board of Directors

SOUTH SAN FRANCISCO, Calif., January 11, 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 that Nancy Thornberry has joined the Board of Directors, effective January 8, 2021. Ms. Thornberry's extensive biotech leadership and pharmaceutical experience includes more than 30 years of development and discovery work in multiple disease areas, including diabetes and endocrinology.

"I'm excited to welcome Nancy to the Board," said Ryan Watts, Ph.D., Denali's Chief Executive Officer. "Nancy's industry experience spans all stages of pharmaceutical development from the discovery of new molecular entities to clinical research leading to the approval of important new classes of medicines. Her perspective will be an asset as we continue to advance a broad portfolio of therapeutic candidates to treat neurodegeneration."

"It's an honor to join Denali's Board of Directors," said Ms. Thornberry. "With a singular focus on neurodegeneration, Denali is tackling one of the biggest medical challenges that our society faces today. I am impressed with the breadth of Denali's pipeline and the vast opportunities afforded by its platform technology for delivering biotherapeutics to the brain. I look forward to applying my insights as a drug developer towards Denali's continued growth and success."

Ms. Thornberry is Chief Executive Officer of Kallyope. She was formerly Senior Vice President and Franchise Head, Diabetes and Endocrinology, Merck & Co. Inc. In this role she led discovery and clinical research in diabetes, osteoporosis, fertility, and contraception. Prior to her role as Franchise Head, she initiated and was a leader of Merck's dipeptidyl peptidase 4 (DPP-4) project, which resulted in the discovery of JANUVIA® for the treatment of Type 2 diabetes. Among other notable scientific accomplishments is the identification of the first caspase, interleukin-1β converting enzyme (ICE/caspase-1). For her scientific contributions Ms. Thornberry has received numerous awards, including the Merck Presidential Fellowship, Merck Directors Award, Heroes of Chemistry Award by the American Chemical Society, and in 2011 received the Pharmaceuticals Research and Manufacturers of America (PhRMA) Discoverers Award, which honors research scientists whose work has been of special benefit to humankind.

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

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Denali Therapeutics Announces Significant Program Progress and Expected Key Milestones in 2021 for Its Broad Therapeutic Portfolio in Neurodegeneration

- *Late-breaker presentation on 12-week data from Cohort A in Phase 1/2 study of DNL310 (ETV:IDS) in Hunter syndrome (MPS II) to be held at WORLD Symposium on February 12th*
- *Following previously announced data on CSF GAG reduction with DNL310 and achievement of biomarker proof-of-concept, Phase 1/2 study is expanded with the addition of a third cohort (Cohort C) to further explore clinical endpoints*
- *Announcing five new enzyme replacement therapy programs in Transport Vehicle (TV) portfolio; expanding manufacturing capabilities and building out commercial capabilities*
- *Phase 1b study of LRRK2 inhibitor, DNL151 (BIIB122), in Parkinson's disease is complete; target engagement and pathway engagement goals were met and data will be presented at an upcoming medical congress; late-stage clinical development to begin by year-end 2021 in collaboration with Biogen*
- *Phase 1 healthy subject data on EIF2B activator, DNL343, expected to be available in 1H 2021; Phase 1b study in ALS patients planned to begin in 2H 2021*
- *Phase 1 study of CNS-penetrant RIPK1 inhibitor, DNL788 (SAR443820), initiated by Sanofi in Q4 2020; Phase 2 study of peripherally-restricted RIPK1 inhibitor, DNL758 (SAR443122), in cutaneous lupus erythematosus to begin in early 2021*
- *IND-enabling studies for PTV:PRGN and ATV:TREM2 to trigger two milestone payments from Takeda in Q1 2021*

SOUTH SAN FRANCISCO, Calif., Jan. 8, 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 program progress and expected milestones for 2021, which Chief Executive Officer, Ryan Watts, Ph.D., will highlight during a corporate presentation at the 39th Annual J.P. Morgan Healthcare Conference on Tuesday, January 12, at 10 a.m. Eastern Time.

"We begin the year with exciting momentum building off multiple achievements in 2020 including first-in-human biomarker proof-of-concept for our proprietary Transport Vehicle (TV) technology to deliver biotherapeutics to the brain and progression of our LRRK2 program to late-stage clinical development in collaboration with Biogen," said Dr. Watts. "We expect 2021 to be a year of significant growth for Denali on our path to becoming a fully integrated discovery, development and commercial organization. Our near-term focus is to advance our first product candidates towards late-stage clinical development; continue to develop our TV portfolio, including five new Enzyme TV (ETV) programs; expand manufacturing capabilities; and continue to build out commercial capabilities to serve patients and deliver the full potential of our pipeline."

Denali's 2021 Outlook

Denali's therapeutic portfolio includes small molecules designed to cross the BBB and biotherapeutics that are enabled to cross the BBB using Denali's TV technology. Expected progress and key milestones in 2021 across Denali's therapeutic portfolio are summarized below.

Expanding Phase 1/2 study of ETV:IDS (DNL310) in Hunter syndrome (MPS II)

Denali's lead TV-enabled program is ETV:IDS (DNL310) for the potential treatment of Hunter syndrome (MPS II). In November 2020, Denali announced positive biomarker proof-of-concept data from five patients enrolled in Cohort A, who received four weekly intravenous doses of DNL310, showing a statistically significant reduction in levels of glycosaminoglycans (GAGs) as measured in the cerebrospinal fluid (CSF), with normal healthy levels being achieved in four of five patients.

The ongoing Phase 1/2 study is progressing as per plan, with dose escalation in Cohort A completed and patient enrollment initiated in Cohort B. New data from Cohort A after 12 weeks of treatment will be presented in a late-breaker presentation at the WORLD Symposium on February 12th. Based on strong proof-of-concept data, Denali is expanding its DNL310 development program by adding a third cohort (Cohort C, ~12 patients) to the ongoing Phase 1/2 study, which will enable further exploration of clinical endpoints related to neuronopathic manifestations in patients. Denali plans to initiate a Phase 2/3 study in 1H 2022.

Expanding Denali's TV portfolio and announcing five new ETV programs for lysosomal storage diseases

More than 30,000 patients suffer from lysosomal storage diseases world-wide, with approximately two-thirds having CNS manifestations that are not addressed by currently available enzyme replacement therapies. Following achievement of human biomarker proof-of-concept with ETV:IDS (DNL310) for Hunter syndrome, Denali is expanding the development of its current ETV programs including DNL310 (as described above) and ETV:SGSH for MPS IIIA. In addition, Denali is announcing five new brain-penetrant enzyme replacement therapy programs in its ETV portfolio including: (1) ETV:GBA for Gaucher disease and Parkinson's disease; (2) ETV:GAA for Pompe disease; (3) ETV:IDUA for MPS I; (4) ETV:NAGLU for MPS IIIB; and (5) ETV:ARSA for MLD. Activities are underway to expand manufacturing capabilities and continue to build out commercial capabilities.

Advancing the first LRRK2 inhibitor into late-stage clinical development for Parkinson's disease

In August 2020, Denali and Biogen announced a collaboration to co-develop and co-commercialize Denali's small molecule inhibitors of leucine-rich repeat kinase 2 (LRRK2) for Parkinson's disease. Denali has evaluated two LRRK2 inhibitors, DNL201 and DNL151 (BIIB122), in more than 300 healthy volunteers and Parkinson's patients who participated in Phase 1 and Phase 1b studies. As previously announced, DNL151 was selected by Denali and Biogen as the lead molecule to advance into late-stage clinical development with DNL201 as a backup. A Phase 1b study in Parkinson's patients is complete; target engagement and pathway engagement goals were met. Denali will present data from the Phase 1b study at upcoming medical congresses. Denali is currently completing further dose escalation cohorts in an expanded Phase 1 study to define the full therapeutic window of DNL151. The companies expect to initiate late-stage clinical development of DNL151 in Parkinson's patients by year-end 2021. Two clinical studies are planned: one in patients who carry LRRK2 mutations and the other in patients who have idiopathic disease.

Initiating the first clinical study of an EIF2B activator in amyotrophic lateral sclerosis (ALS)

Mutations in genes associated with ALS and frontotemporal dementia (FTD) alter RNA homeostasis, which contributes to the aggregation on TDP-43 or other RNA binding proteins observed in a large proportion of patients. Activators of EIF2B have demonstrated benefits in resolving TDP-43 aggregation, restoring protein translation and attenuating neurodegeneration via inhibition of the cellular integrated stress response in numerous *in vitro* and *in vivo* models. Denali's most advanced EIF2B activator, DNL343, is a brain-penetrant small molecule designed to rescue EIF2B function and restore normal RNA metabolism. Results from a Phase 1 study of DNL343 in healthy volunteers are expected to be available in 1H 2021. Denali plans to initiate a Phase 1b study of DNL343 in patients with ALS in 2H 2021.

Advancing RIPK1 inhibitors for neurodegenerative and peripheral inflammatory diseases

Denali has a strategic collaboration with Sanofi for the development of small molecules that inhibit receptor interacting serine/threonine protein kinase 1 (RIPK1). RIPK1 is a critical signaling protein in the tumor necrosis factor (TNF) receptor pathway and is a regulator of inflammation and cell death. In Q4 2020, Sanofi initiated a Phase 1 healthy volunteer study of DNL788 (SAR443820), a potent, selective, and brain-penetrant small molecule RIPK1 inhibitor intended to treat patients with ALS, Alzheimer's disease, and multiple sclerosis; data is expected to be available in 2H 2021. The collaboration with Sanofi also includes peripherally-restricted RIPK1 inhibitors. Denali previously announced that Sanofi completed enrollment in a Phase 1b clinical trial of DNL758 (SAR443122), a peripherally-restricted small molecule inhibitor of RIPK1, in hospitalized adult patients with severe COVID-19 lung disease. In addition, Sanofi plans to initiate a Phase 2 clinical trial of DNL758 in patients with cutaneous lupus erythematosus in early 2021.

Advancing additional TV-enabled modalities towards clinical development

DNL593 (PTV:PGRN), an intravenously administered recombinant progranulin biotherapeutic enabled by Denali's Protein Transport Vehicle (PTV), is designed to restore normal levels of progranulin in multiple cell types in the brain for the potential treatment of FTD. In December 2020, Denali initiated IND-enabling studies for DNL593 for which Denali will receive a related milestone payment of $8 million from Takeda. Denali plans to file an IND application or a clinical trial application (CTA) in late 2021.

DNL919 (ATV:TREM2), an intravenously administered antibody enabled by Denali's Antibody Transport Vehicle (ATV), is designed to modulate TREM2 and normalize microglial function for the potential treatment of Alzheimer's disease. Denali expects to initiate IND-enabling studies for DNL919 in January 2021 and for which Denali will receive a related milestone payment of $8 million from Takeda. Denali plans to file an IND application or a CTA in late 2021/early 2022.

Summary Table of 2021 Expected Key Milestones

Timing	**Investigational Drug Candidate**	**Therapeutic Area**	**Expected Milestone**
Q1	ETV:IDS (DNL310)	Hunter syndrome (MPS II)	Late-breaker presentation on 12-week data from Cohort A in Phase 1/2 study at WORLD Symposium
Q1	PTV:PGRN (DNL593)	frontotemporal dementia (FTD)	Receive milestone payment from Takeda for initiation of IND-enabling studies
Q1	ATV:TREM2 (DNL919)	Alzheimer's disease	Receive milestone payment from Takeda for initiation of IND-enabling studies
1H	RIPK1 inhibitor (DNL758)	inflammatory diseases, COVID-19	Initiate Phase 2 study in cutaneous lupus erythematosus patients (Sanofi); Phase 1b data in COVID-19 (Sanofi)
1H	EIF2B activator (DNL343)	amyotrophic lateral sclerosis (ALS), FTD	Phase 1 data in healthy volunteers
Mid 2021	ETV:IDS (DNL310)	Hunter syndrome (MPS II)	24-week data from Cohort A of Phase 1/2 study
2H	EIF2B activator (DNL343)	ALS, FTD	Initiate Phase 1b study in ALS patients
2H	RIPK1 inhibitor (DNL788)	ALS, Alzheimer's disease, multiple sclerosis	Phase 1 data in healthy volunteers
Late 2021	LRRK2 inhibitor (DNL151)	Parkinson's disease	Initiate late-stage clinical development
Late 2021	PTV:PRGN (DNL593)	FTD	File IND application or CTA
Late 2021/ Early 2022	ATV:TREM2 (DNL919)	Alzheimer's disease	File IND application or CTA

Webcast and slide deck for Denali's corporate presentation at the J.P. Morgan Healthcare Conference

A webcast of Dr. Watts' presentation during the J.P. Morgan Conference as well as a PDF of the related slide deck will be available on the Events page under the Investor section of the Denali's website at https://www.denalitherapeutics.com/investors/events. An archived replay of the presentation will be available for approximately 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 business strategy, business plans, product candidates, planned preclinical studies and clinical trials; expectations regarding the timing of results of such studies and trials; plans, timelines and expectations related to DNL151 and other LRRK2 inhibitor molecules; 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; plans, timelines and expectations related to DNL343, including with respect to the availability of data and the initiation of future clinical trials; plans, timelines and expectations related to DNL788 and DNL758 of both Denali and Sanofi, including with respect to the availability of data and the initiation of future clinical trials; Denali's expectations regarding DNL593 and DNL919 and plans and expectations regarding planned regulatory filings and milestone payments with respect to such programs; Denali's priorities, regulatory approvals, timing and likelihood of success and expectations regarding collaborations; and statements made by Denali's 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 collaborators; Denali's early stages of clinical drug development; Denali's and its collaborators' ability to complete the development and, if approved, commercialization of its product candidates; Denali's and its collaborators' 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 collaborators' ability to conduct or complete clinical trials on expected timelines; the risk that preclinical profiles of Denali's product candidates may not translate in clinical trials; the potential for clinical trials of Denali's product candidates to differ from preclinical, early clinical, preliminary or expected results; the uncertainty that product candidates will receive regulatory approval necessary to be commercialized; 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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