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 17, 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 7.01 Regulation FD Disclosure.

On November 17, 2021, Denali Therapeutics Inc. (the "Company") issued a press release announcing that Takeda Pharmaceutical Company Limited ("Takeda") has exercised its option, pursuant to an existing collaboration agreement between the two companies, to co-develop and co-commercialize DNL593 (PTV:PGRN), an investigational, brain-penetrant progranulin replacement therapy for the potential treatment of frontotemporal dementia-granulin (FTD-GRN).

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

The information furnished in this Item 7.01 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 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 November 17, 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: November 17, 2021

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

Denali Therapeutics Announces Strategic Partner Takeda Exercises Option to Co-Develop and Co-Commercialize DNL593 (PTV:PGRN)

— Companies to advance clinical development of DNL593 as a brain-penetrant progranulin replacement therapy for frontotemporal dementia-granulin (FTD-GRN) —

SOUTH SAN FRANCISCO, Calif., November 17, 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 its strategic partner Takeda Pharmaceutical Company Limited ("Takeda") has exercised an option, pursuant to an existing collaboration agreement between the two companies, to co-develop and co-commercialize DNL593 (PTV:PGRN), an investigational, brain-penetrant progranulin replacement therapy for the potential treatment of frontotemporal dementia-granulin (FTD-GRN).

"We are excited to advance our collaboration with Takeda on the development of DNL593 as a potential treatment for people with FTD-GRN," said Denali's Chief Executive Officer, Ryan Watts, Ph.D. "Pending acceptance of regulatory submissions, DNL593 will be the sixth therapeutic candidate from our broad pipeline, and our second Transport Vehicle (TV)-enabled molecule, in clinical development. This progress underscores the potential of our TV platform technology, which is designed to enable and enhance delivery of biologic therapeutics to the brain for the treatment of neurodegenerative diseases."

"At Takeda, our focus is to develop transformative treatments for patients suffering from devastating neurologic disorders. One of the main challenges in the development of these medicines is to achieve adequate biodistribution in target tissues, and Denali has engineered a promising TV platform technology to transport biologic therapeutics across the BBB and into the brain," said Sarah Sheikh, BM BCh, MSc, MRCP, Head, Neuroscience Therapeutic Area Unit at Takeda. "Preclinical studies with DNL593 are encouraging and demonstrate that Protein Transport Vehicle (PTV) can enhance the uptake of peripherally administered progranulin (PGRN) by multiple cell types in the brain, including neurons and microglia. We look forward to working with Denali to deliver DNL593 as a potentially transformative treatment for people living with FTD-GRN."

In January 2018, Denali and Takeda entered into a collaboration agreement, pursuant to which Takeda was granted an option for three programs including PTV:PGRN. By exercising its option to the PTV:PGRN program, Takeda obtains the right to develop and commercialize DNL593 jointly with Denali. Denali will receive an option fee and may also receive future milestone payments upon achievement of certain clinical and regulatory milestone events as well as certain sales-based milestones. Subject to the terms of the collaboration agreement, the companies will share the development and commercialization costs equally, and, if applicable, profits on a worldwide basis.

About Frontotemporal Dementia (FTD)

FTD is the most common form of dementia in people under 60 years of age. While the progression of symptoms varies by individual, FTD brings an inevitable decline in function together with changes in personality and social behaviors, and sometimes language and/or motor dysfunction. Mutations in the granulin (*GRN*) gene, which encodes the progranulin (PGRN) protein, generally result in reduced levels of PGRN and are amongst the most common genetic causes of FTD. There are currently no approved medications to stop or slow the progression of FTD or FTD-GRN.

About DNL593 (PTV:PGRN)

DNL593 is an investigational, intravenously administered, brain-penetrant progranulin (PGRN) replacement therapy enabled by Denali's Protein Transport Vehicle (PTV) technology. PGRN is known to promote lysosomal function, in addition to having neurotrophic and anti-inflammatory effects. Data from *in vitro* and *in vivo* models providing nonclinical proof of concept for DNL593 were published in the September 2, 2021, issue of the scientific journal *Cell*. The studies demonstrated that DNL593 enhanced brain uptake of peripherally administered PGRN by multiple cell types in the brain, including neurons and microglia. In addition, DNL593 rescued both neurodegeneration and microglial dysfunction in PGRN-deficient mice. These nonclinical data support the potential for DNL593 to increase PGRN levels in the brain and impact disease progression of FTD-GRN.

DNL593 has not been approved by any Health Authority. Denali plans to submit a clinical trial application (CTA) with the Medicines and Healthcare products Regulatory Agency (MHRA) for DNL593 in the fourth quarter of 2021.

About Denali's TV 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 diseases of the central nervous system (CNS) 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 enabled by 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 business strategy, business plans and product candidates; plans, timelines, and expectations related to DNL593 of both Denali and Takeda, including with respect to its potential utility in treating certain types of frontotemporal dementia and the initiation of future clinical trials, and plans, timing, and expectations regarding planned regulatory filings and milestone payments with regard to this product candidate; plans, timelines and expectations related to Denali's TV technology platform and other programs enabled by Denali's TV platform; Denali's priorities, regulatory approvals, timing, and likelihood of success and expectations regarding the collaboration with Takeda; 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: any and all risks to Denali's business and operations caused directly or indirectly by the evolving COVID-19 pandemic; Denali's early stages of clinical drug development; Denali's ability to complete the development and, if approved, commercialization of its product candidates; Denali's ability to realize the therapeutic efficacy of its TV technology in human models as well as animal models; Denali's 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 risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's collaboration agreements, including the collaboration agreement with Takeda; Denali's dependence on successful development of its BBB platform technology; Denali's ability to conduct or complete clinical trials on expected timelines; the risk that preclinical profiles of Denali's product candidates, such as DNL593, may not translate in clinical studies, the uncertainty that product candidates will receive the regulatory approval necessary to be commercialized; Denali's ability to continue to create a pipeline of product candidates or develop commercially successful products; 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 its product candidates and TV platform technology; implementation of Denali's strategic plans for its business, product candidates and BBB platform technology; Denali's ability to obtain additional capital to finance its operations, as needed; Denali's ability to accurately forecast future financial results in the current environment; general economic and market conditions; and other risks and uncertainties, including those described in Denali's most recent Annual Report on Form 10-K, most recent Quarterly Report on Form 10-Q and Denali's future reports to be filed with the SEC. The forward-looking statements in this press release are based on information available to Denali as of the date hereof. Denali disclaims any obligation to update any forward-looking statements, except as required by law.

Investor Relations Contact:
Laura Hansen, Ph.D.
Vice President, Investor Relations
(650) 452-2747
hansen@dnli.com

Media Contacts:
Lizzie Hyland
(646) 495-2706
lizzie.hyland@fgh.com
or
Morgan Warners
(202) 295-0124
morgan.warners@fgh.com