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 9, 2023

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 January 9, 2023, Denali Therapeutics Inc. (the "Company") issued a press release announcing an update on its programs and expected milestones for 2023 and the Company's participation in the 41st Annual J.P. Morgan Healthcare Conference.

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 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 January 9, 2023.
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 9, 2023

By: /s/ Alexander O. Schuth
Alexander O. Schuth, M.D.
Chief Operating and Financial Officer

Denali Therapeutics Announces Key Anticipated 2023 Milestones for Its Therapeutic Portfolio for Neurodegeneration and Lysosomal Storage Diseases

- Four programs expected to progress in late-stage clinical studies for MPS II (Hunter syndrome), ALS, and Parkinson's disease
- Further validation and expansion of Transport Vehicle (TV) technology, including multiple interim clinical data readouts, submission of IND for additional ETV program, and selection of five Oligonucleotide TV (OTV) targets
- Continued invention and scientific insights in neurodegeneration biology fuel broad early-stage pipeline of therapeutic candidates

SOUTH SAN FRANCISCO, Calif., Jan. 9, 2023 — 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 and lysosomal storage diseases, today announced program progress and expected milestones for 2023, which Chief Executive Officer, Ryan Watts, Ph.D., will highlight during a corporate presentation at the 41st Annual J.P. Morgan Healthcare Conference on Tuesday, January 10th, at 10:30 a.m. Pacific Time.

"We are excited to kick off 2023 with a broad and diversified therapeutic portfolio of seven programs in clinical development, anticipated progression and expansion of our TV blood-brain barrier platform technology, and a highly productive discovery organization working to capture and translate the potential of new scientific insights in neurodegeneration biology," said Dr. Watts. "With four programs expected to be in late-stage development this year, we continue to build commercial capabilities and expand our global footprint to ultimately deliver effective medicines to people living with neurodegenerative and lysosomal storage diseases."

Denali's 2023 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 2023 across Denali's therapeutic portfolio are summarized below.

TV-ENABLED PROGRAMS

DNL310 (ETV:IDS): MPS II (Hunter syndrome)

DNL310 is an investigational, Enzyme Transport Vehicle (ETV)-enabled, brain-penetrant iduronate-2-sulfatase (IDS) replacement therapy designed to address the cognitive, behavioral, and physical manifestations of MPS II (Hunter syndrome). Delivery of the IDS enzyme to the brain addresses a significant unmet therapeutic need as current enzyme replacement therapy does not address neurocognitive manifestations of the disease.

As previously reported, interim Phase 1/2 study data up to one year of treatment continued to show that once weekly intravenous dosing with DNL310 led to rapid and sustained normalization to healthy levels of heparan sulfate in cerebrospinal fluid (CSF) and improvements in biomarkers of lysosomal function consistent with durable central nervous system activity. The safety profile, with up to 85 weeks of dosing, continued to be consistent with approved enzyme replacement therapies. In addition, one-year exploratory outcomes data from clinician and caregiver global impression scales of change suggested that the majority of study participants improved or stabilized compared to baseline.

The Phase 2/3 COMPASS study continues to recruit up to 54 participants with MPS II with and without neuronopathic disease. Upon completion of the ongoing Phase 1/2 study, and together with data from the global COMPASS study, this combined data package is intended to support registration.

2023 expected progress and milestones:

- Presentation of additional interim Phase 1/2 data at World*Symposium* (February 22-26) and at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium (August 29-September 1).
- Continued recruitment of participants with MPS II in the global Phase 2/3 COMPASS study.

TAK-594/DNL593 (PTV:PGRN): Frontotemporal dementia-granulin (FTD-GRN)

TAK-594/DNL593 (PTV:PGRN) is an investigational, Protein Transport Vehicle (PTV)-enabled, brain-penetrant progranulin (PGRN) replacement therapy for people with FTD-GRN. As previously reported, interim results from Part A of the Phase 1/2 study evaluating DNL593 in healthy subjects demonstrated that single doses of DNL593 resulted in substantial increases in CSF PGRN levels suggesting brain delivery of DNL593 was achieved and has the potential to address PGRN deficiency, which drives FTD-GRN disease progression. Single doses of DNL593 were generally well tolerated, based on blinded safety analysis. These data support dosing in participants with FTD-GRN in Part B (ascending multiple doses) of the study. Denali has a strategic collaboration with Takeda to jointly develop and commercialize PGRN delivering PTV-based molecules.

2023 expected progress and milestones:

- Final data from Phase 1/2 Part A healthy volunteer study in mid 2023.
- Continued recruitment of participants with FTD-GRN in Part B of the Phase 1/2 study.

TAK-920/DNL919 (ATV:TREM2): Alzheimer's disease (AD)

TAK-920/DNL919 (ATV:TREM2) is an investigational, Antibody Transport Vehicle (ATV)-enabled, brain-penetrant TREM2 agonist intended to improve microglial function as a potential treatment for AD. TREM2 is a receptor expressed on microglia, the resident immune cells of the brain. Loss-of-function TREM2 genetic mutations are strongly associated with an increased risk for AD. Animal model data demonstrate enhanced brain uptake and improved pharmacodynamic response with DNL919 as compared to a non-ATV TREM2 antibody. A Phase 1 single ascending dose study in healthy volunteers is ongoing in the Netherlands. Denali has a strategic collaboration with Takeda to jointly develop and commercialize TREM2 targeting ATV-based molecules.

2023 expected progress and milestones:

- Data from the Phase 1 single ascending dose study in healthy volunteers by year-end 2023.

DNL126 (ETV:SGSH): MPS IIIA (Sanfilippo syndrome Type A)

DNL126 (ETV:SGSH) is Denali's second most advanced ETV program following DNL310 (ETV:IDS). DNL126 is in development for the potential treatment of MPS IIIA (Sanfilippo syndrome Type A), a rare lysosomal storage disease that causes neurodegeneration. MPS IIIA is caused by genetic defects that result in a reduction in the activity of N-sulfoglucosamine sulfohydrolase (SGSH), an enzyme responsible for degrading heparan sulfate in the lysosome. There are no approved treatments for MPS IIIA. Preclinical data demonstrated that intravenous DNL126 treatment reduced heparan sulfate in a dose-dependent manner in brain and CSF in an MPS IIIA mouse model.

2023 expected progress and milestones:

- Preclinical data at WORLD*Symposium* (February 22-26).
- Submission of an investigational new drug (IND) application in the first half and Phase 1/2 recruitment activities in the second half of 2023.

Oligonucleotide Transport Vehicle (OTV) platform

Oligonucleotides, such as antisense oligonucleotides (ASOs), are a novel class of biotherapeutics with the potential to address the root cause of many diseases through modulation of gene expression. This class, however, has been limited in its potential for treatment of neurodegenerative diseases, primarily due to the challenge of delivering effective amounts of drug to relevant brain regions. Direct injection into the CSF (e.g., intrathecal injection) or certain brain regions has not achieved the robust biodistribution into deep brain tissue, which may be necessary for effective therapeutic activity.

As previously reported, nonhuman primate data with Denali's OTV demonstrated that intravenous delivery of an ASO enabled by OTV technology resulted in broad brain biodistribution of the ASO and knockdown of target gene expression in all brain cell types, which was superior to intrathecal administration of the ASO. These data support the potential of the OTV platform to enable peripheral administration of oligonucleotide therapeutics and to address a wide range of neurodegenerative and other neurological diseases. Denali has selected five ASO targets for further development with a near-term focus on advancing two OTV candidates towards clinical development.

SMALL MOLECULE PROGRAMS

BIIB122/DNL151 (LRRK2 inhibitor): Parkinson's disease (idiopathic and LRKK2-positive)

BIIB122/DNL151 is a small molecule inhibitor of LRRK2, which may have the ability to restore impaired lysosomal function, which is implicated in Parkinson's disease (PD) pathology and disease progression. BIIB122/DNL151 is the most clinically advanced small molecule inhibitor of LRRK2 currently in clinical testing for PD.

Results from Phase 1 and Phase 1b trials of BIIB122 in healthy volunteers and patients with PD, respectively, showed robust target and pathway engagement as measured by pS935 LRRK2 and pT73 Rab10, respectively. In addition, a dose-dependent reduction in urine of the lysosomal lipid 22:6-bis[monoacylglycerol] phosphate (BMP), a biomarker of lysosomal function, was achieved with BIIB122 treatment, providing evidence supporting improvement of lysosomal function. BIIB122 was generally well tolerated across a broad range of doses for up to 28 days, the longest treatment duration in both studies.

Denali has a strategic collaboration with Biogen to jointly develop and commercialize small molecule inhibitors of LRRK2. Biogen is conducting two global late-stage clinical trials of BIIB122: the Phase 2b LUMA study, which commenced in May 2022 in approximately 640 participants with early-stage PD; and the Phase 3 LIGHTHOUSE study, which commenced in September 2022 in approximately 400 participants with PD with a confirmed LRRK2 pathogenic variant. Both studies are evaluating the efficacy and safety of BIIB122 as compared to placebo.

2023 expected progress and milestones:

- Continued recruitment of participants with PD in the Phase 2b LUMA and Phase 3 LIGHTHOUSE studies.

SAR443820/DNL788 (CNS-penetrant RIPK1 inhibitor): ALS, MS, AD

SAR443820/DNL788 is a small molecule inhibitor of RIPK1, a critical signaling protein in a canonical inflammatory and cell death pathway. Increased RIPK1 activity in the brain drives neuroinflammation and cell necroptosis and contributes to neurodegeneration. RIPK1 inhibition has been shown to have beneficial effects in preclinical models of amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Alzheimer's disease (AD), and other diseases.

Denali has a strategic collaboration with Sanofi to jointly develop and commercialize small molecules that inhibit RIPK1. In 2022, Sanofi commenced dosing in the HIMALAYA global Phase 2 study of SAR443820 and expects to enroll approximately 260 participants with ALS. A Phase 2 study in MS is also planned. Denali is leading preclinical research on SAR443820 as a potential treatment for AD.

2023 expected progress and milestones:

- Initiation of Phase 2 study in MS in early 2023.
- Completion of recruitment of participants with ALS in the Phase 2 HIMALAYA study.

DNL343 (eIF2B activator): ALS

DNL343 is a small molecule activator of the eukaryotic initiation factor 2B (eIF2B) with first-in-class potential for the treatment of ALS and other indications. DNL343 is designed to inhibit the cellular integrated stress response (ISR) to prevent or slow disease progression that is associated with stress granule formation and TDP-43 aggregation, a hallmark pathology present in nearly all individuals with ALS.

Denali is conducting a Phase 1b multicenter, randomized, placebo-controlled, double-blind, 28-day study followed by an 18-month open-label extension, designed to evaluate the safety, pharmacokinetics, and pharmacodynamics of DNL343 in participants with ALS. Enrollment in the study is complete with 29 participants. As previously reported, an interim analysis was performed after 20 participants randomized to receive DNL343 or placebo had completed the double-blind period of the study. The interim results demonstrated that once-daily oral dosing with DNL343 for 28 days was generally well tolerated and demonstrated extensive BBB penetration as well as robust inhibition of biomarkers associated with the ISR pathway in blood samples from study participants. The interim data continue to support late-stage development of DNL343; as previously announced, the design phase of the Phase 2/3 study of DNL343 is underway for entry into the HEALEY ALS Platform Trial led by the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital (MGH) in collaboration with the Northeast ALS Consortium.

2023 expected progress and milestones:

- Final data from the 28-day double-blind, placebo-controlled portion of the Phase 1b study in mid 2023.
- Initiation of Phase 2/3 study in the HEALEY ALS Platform Trial in mid 2023.

OTHER CLINICAL PROGRAMS

SAR443122/DNL758 (peripherally-restricted RIPK1 inhibitor): CLE and UC

Denali's collaboration with Sanofi also includes the peripherally-restricted RIPK1 inhibitor SAR443122/DNL758 (eclitasertib), which is currently being evaluated in a Phase 2 trial in patients with cutaneous lupus erythematosus (CLE). Today Denali announced that Sanofi has initiated a Phase 2 trial of SAR443122 in patients with ulcerative colitis (UC). Sanofi is solely responsible for the development and commercialization of peripherally restricted RIPK1 inhibitors.

2023 expected progress and milestones:

- Primary completion of Phase 2 CLE study in June 2023.
- Continued recruitment of participants with ulcerative colitis in the Phase 2 study.

DISCOVERY PROGRAMS

Denali continues to advance a broad preclinical portfolio including programs enabled by the Enzyme Transport Vehicle, the Antibody Transport Vehicle, and the Oligonucleotide Transport Vehicle, and several small molecules engineered to cross the BBB and intended as potential treatments for patients with neurodegenerative diseases and lysosomal storage diseases.

Today Denali announced that new research will be presented at the upcoming inaugural Keystone Symposium on 'Drug Delivery to the Brain: Challenges and Progress', which is being held January 23-26, 2023, in Breckenridge, Colorado, including expansion of the TV technology to utilize an additional BBB transporter and potential TV applications in oncology.

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's TV Platform

The blood-brain barrier is essential in maintaining the brain's microenvironment and protecting it from harmful substances and pathogens circulating in the bloodstream. Historically, the blood-brain barrier has posed significant challenges to drug development for central nervous system diseases by preventing most drugs from reaching the brain in therapeutically relevant concentrations. Denali's Transport Vehicle platform is a proprietary technology designed to effectively deliver large therapeutic molecules such as antibodies, enzymes, proteins, and oligonucleotides across the blood-brain barrier after intravenous administration. The Transport Vehicle technology is based on engineered Fc domains that bind to specific natural transport receptors, such as transferrin receptor, which are expressed at the blood-brain barrier and are designed to deliver the Transport Vehicle and its therapeutic cargo to the brain through receptor-mediated transcytosis. In animal models, antibodies and enzymes engineered with the Transport Vehicle 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 BBB for neurodegenerative diseases and lysosomal storage disorders. 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, expected progress and key milestones for Denali's therapeutic portfolio in 2023; expectations relating to the potential for Denali's product candidates to treat various neurodegenerative and lysosomal storage diseases including MPS II (Hunter Syndrome), ALS, PD, AD, FTD-GRN, MPS IIIA (Sanfilippo syndrome Type A) and related peripheral inflammatory diseases; planned preclinical studies and clinical trials relating to the pipeline of product candidates; expectations regarding the timing of results and data from such studies and trials; timelines, plans, and expectations relating to Denali's Transport Vehicle (TV) platform, including its Antibody Transport Vehicle (ATV), Protein Transport Vehicle (PTV), Oligonucleotide TV (OTV) and Enzyme Transport Vehicle (ETV) technologies; plans, timelines and expectations relating to the Phase 1/2 and Phase 2/3 trials and enrollment of the Phase 2/3 trial of DNL310, as well as subsequent registration; plans, timelines, and expectations relating to the development of DNL593, including the Phase 1/2 Part A and Part B trials; plans, timelines and expectations relating to the development of DNL919, including the Phase 1 healthy volunteer trial; plans, timelines, and expectations relating to DNL126 and its potential to treat MPS IIIA, as well as the Phase 1/2 trials and planned regulatory filings; plans, timelines and expectations relating to the Biogen-led development of LRRK2 inhibitor DNL151, including the global Phase 2b trial and global Phase 3 trial; plans, timelines and expectations relating to the Sanofi-led development of DNL788, including Phase 2 trials in ALS and MS and preclinical exploration of potential treatment of AD; plans, timelines and expectations regarding the Phase 1b and Phase 2/3 trials of DNL343; plans, timelines and expectations relating to the Sanofi-led development of DNL758, including Phase 2 trials in CLE and ulcerative colitis; plans, timelines and expectations relating to expansion of the TV technology to utilize an additional BBB transporter and potential TV applications in oncology; plans and expectations with respect to Denali's collaborations with Biogen, Sanofi and 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, 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 its programs and product candidates; Denali's and its collaborators' ability to conduct or complete clinical trials on expected timelines; the risk of significant adverse events, toxicities or other undesirable side effects; the risk that preclinical profiles of Denali's product candidates may not translate in clinical trials, including risks related to the predictive ability of nonhuman data; 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 attract, motivate and retain qualified managerial, scientific and medical personnel; 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; implementation of Denali's strategic plans for its business, product candidates and blood-brain barrier 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. 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 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 28, 2022 and November 3, 2022, 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.

Investor Relations Contact:

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

Media Contact:

dna Communications Angela Salerno-Robin
Senior Vice President, Media Relations, Healthcare
(212) 445-8219
Asalerno-robin@dna-comms.com