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 28, 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 2.02 Results of Operations and Financial Condition.

On February 28, 2022, Denali Therapeutics Inc. (the "Company") issued a press release announcing its financial results for the fourth quarter ended December 31, 2021. The full text of the press release is attached hereto as Exhibit 99.1 and is incorporated herein by reference.

All of the information furnished in this Item 2.02 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, and shall not be incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, 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 28, 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 28, 2022

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

Denali Therapeutics Reports Fourth Quarter and Full Year 2021 Financial Results and Business Highlights

SOUTH SAN FRANCISCO – February 28, 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 reported financial results for the fourth quarter and year ended December 31, 2021, and provided business highlights.

“Denali is now transitioning to a late-stage development company, having made significant progress in advancing our clinical portfolio of product candidates for neurodegenerative and lysosomal storage diseases during 2021,” said Ryan Watts, Ph.D., Denali’s Chief Executive Officer. “In 2022, we plan to advance DNL151 and DNL310 into potentially registrational clinical trials for Parkinson’s disease and MPS II (Hunter syndrome), respectively, as well as DNL788 into a Phase 2 trial for ALS. We are advancing new Transport Vehicle (TV) programs into the clinic, starting with DNL593 (PTV:PGRN) for FTD-GRN. In addition, we also look forward to generating initial clinical data with our novel eIF2B activator, DNL343, in ALS.”

Recent Program Highlights and Expected Milestones

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

- Announced details on study designs for two late-stage clinical trials of BIIB122/DNL151 in Parkinson’s disease (PD). The LUMA Study is a global Phase 2b trial expected to enroll approximately 640 participants with PD who do not carry a LRRK2 mutation and is designed to potentially support registration of BIIB122. The LIGHTHOUSE Study is a global Phase 3 trial expected to enroll approximately 400 PD participants with LRRK2 mutations.
- Denali’s collaborator Biogen is leading the execution of both the LUMA and LIGHTHOUSE clinical trials for which dosing is expected to begin in 2022.

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

- Presented interim data from the Phase 1/2 clinical trial of DNL310 at the WORLD*Symposium*™ on lysosomal diseases. Longer-term data in 20 patients with MPS II continued to show sustained normalization of CSF heparan sulfate, consistent with durable CNS activity, with up to one year of intravenous dosing with DNL310. DNL310 remained generally well tolerated with a safety profile consistent with standard-of-care enzyme replacement therapy.
- Also at the WORLD*Symposium*™ conference, presented details on a potentially registrational Phase 2/3 clinical trial designed as a two-year study with the goal of demonstrating efficacy and safety in neuronopathic and non-neuronopathic MPS II. The effect of DNL310 on certain neurobehavioral parameters is among planned key efficacy endpoints.
- Today, published preclinical research in the *Journal of Experimental Medicine* demonstrating the importance of molecular architecture to brain uptake and biodistribution of TfR-based delivery of idursulfase in a mouse model of MPS II.
- Denali expects the Phase 2/3 trial to begin dosing in the first half of 2022.

DNL343 (eIF2B activator): ALS

- Announced that recruiting continues in a Phase 1b clinical trial of DNL343 expected to enroll approximately 30 participants with amyotrophic lateral sclerosis (ALS).
- Denali expects that initial safety and biomarker results from the Phase 1b trial will be available in mid-2022.

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

- Announced that Denali collaborator Sanofi plans to begin dosing with SAR443820 in the HIMALAYA Phase 2 trial in participants with ALS in Q1 2022.
- Announced that Sanofi is planning a Phase 2 trial of SAR443820 in multiple sclerosis (MS).

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

- Announced enrollment continues in a Phase 2 trial of SAR443122 in participants with cutaneous lupus erythematosus (CLE), which is being conducted by Sanofi.
- Announced that Sanofi plans to initiate a Phase 2 trial of SAR443122 in ulcerative colitis (UC).

DNL593 (PTV:PGRN): FTD-GRN

- The Medicines & Healthcare products Regulatory Agency (MHRA) approved the Clinical Trial Application (CTA) in the United Kingdom in January 2022, triggering a $12.0 million milestone from Takeda, which was received in February 2022.
- Dosing with DNL593 in healthy volunteers in a Phase 1/2 clinical trial is expected to commence in Q1 2022.
- Pending initial clinical data from the Phase 1 study, Denali expects to begin dosing participants with frontotemporal dementia-granulin (FTD-GRN) in the second half of 2022.

Preclinical Transport Vehicle Programs

- Announced that a formal clinical hold letter on the Investigational New Drug (IND) application for DNL919 (ATV:TREM2) was received. Denali is moving forward to address the FDA's observations related to the preclinical toxicology assessment and to provide the information requested to initiate clinical studies, including proposed changes to the clinical trial protocol, the informed consent form, and the investigator brochure. Denali expects a delay of at least 3 months to its plans to begin dosing in a first-in-human clinical trial of DNL919. Denali intends to provide an update once a clear path forward has been established.
- Announced preclinical data demonstrating that DNL126 (ETV:SGSH) reduces heparan sulfate in a dose-dependent manner in brain and cerebrospinal fluid in an MPS IIIA mouse model. Denali plans to submit a regulatory application for DNL126 in the first half of 2023.
- Announced the first nonhuman primate data with Denali's Oligonucleotide Transport Vehicle (OTV) delivery platform supporting the potential of the OTV platform to enable superior biodistribution of antisense oligonucleotides (ASOs) across brain regions, provide superior knockdown of target gene expression across all CNS cell types, and enable peripheral dosing.
- Announced new preclinical data with a bispecific ATV:HER2 antibody supporting the potential for ATV:HER2 to treat HER2-positive peripheral tumors and brain metastases and further validating the potential for TV applications in oncology. Denali plans to submit a regulatory application for a lead ATV:HER2 product candidate in 2023.

Recent Corporate Highlights

- Announced the appointment of Erik Harris to the Board of Directors. Mr. Harris is currently serving as Chief Commercial Officer at Ultragenyx and has extensive experience in launching multiple novel medicines across therapeutic areas including neurology and rare diseases.

2022 Guidance on Operating Expenses

- Cash, cash equivalents, and marketable securities were $1.3 billion as of December 31, 2021. For 2022, Denali anticipates an increase of approximately 25-30% in cash operating expenses compared to 2021, offset by approximately $100 million from incoming cash and milestones from Denali's current partnerships.

Participation in Upcoming Investor Conferences

- Oppenheimer 32nd Annual Healthcare Conference, March 15-17
- 1st Annual Needham Virtual Neuroscience Forum, March 16
- Stifel 2022 Virtual CNS Day, March 28-29

Fourth Quarter and Full Year 2021 Financial Results

Net losses were $75.3 million and $290.6 million for the quarter and year ended December 31, 2021, compared to net income of $244.9 million and $71.1 million for the quarter and year ended December 31, 2020, respectively.

Collaboration revenue was $12.5 million and $48.7 million for the quarter and year ended December 31, 2021, compared to $316.8 million and $335.7 million for the quarter and year ended December 31, 2020, respectively. The decrease of $304.3 million and $287.0 million for the quarter and year ended December 31, 2021, respectively, compared to the same periods ended December 31, 2020 were primarily due to a decrease in revenue recognized under the Biogen collaboration agreement partially offset by increases in revenue recognized under collaboration agreements with Takeda and Sanofi.

Total research and development expenses were $67.9 million and $265.3 million for the quarter and year ended December 31, 2021, compared to $54.7 million and $212.6 million for the quarter and year ended December 31, 2020, respectively. The increases of approximately $13.2 million and $52.7 million for the quarter and year ended December 31, 2021, respectively, were primarily attributable to an increase in personnel-related expenses, including stock-based compensation, driven primarily by higher headcount and equity award grants. Additionally, there were increases in external expenses related to progression of Denali's portfolio, including costs related to the progress of the eIF2B and ETV:IDS programs in the clinic in 2021 and the development of the TV platform reflecting the progress in the PTV:PGRN and ATV:TREM2 programs as well the Company's continued investment in developing a robust pipeline. These increases were partially offset by a decrease in external expenses related to the LRRK2 program primarily due to completion of the Phase 1 and 1b studies, as well as cost sharing reimbursements under the collaboration agreements with Biogen and Takeda.

General and administrative expenses were $21.8 million and $79.1 million for the quarter and year ended December 31, 2021, compared to $18.0 million and $60.3 million for the quarter and year ended December 31, 2020, respectively. The increases of approximately $3.8 million and $18.8 million for the quarter and year ended December 31, 2021, respectively, were primarily attributable to an increase in personnel-related expenses, including stock-based compensation, driven primarily by higher headcount and equity award grants. Additionally, there were increases in other general costs such as insurance, tax, IT and facilities related expenses. These increases were partially offset by a decrease in legal and other professional services expenses as 2020 included expenses associated with the execution of the Biogen collaboration.

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, business plans, business strategy, product candidates, planned preclinical studies and clinical trials and expected milestones; plans to conduct clinical development activities across various programs; plans, timelines and expectations related to Denali's Transport Vehicle (TV) platform, including Denali's Antibody Transport Vehicle (ATV), Protein Transport Vehicle (PTV) and Oligonucleotide Transport Vehicle (OTV) technologies, and regulatory applications for DNL126 and a lead ATV:HER2 product candidate; plans for advancing new TV programs into the clinic for the potential treatment of FTD-GRN and Alzheimer's disease; plans, timelines and expectations regarding DNL151, including with respect to late-stage clinical trials for the treatment of Parkinson's disease in collaboration with Biogen, and patient enrollment and dosing in such trials; plans, timelines and expectations regarding DNL310, including advancement into a potentially registrational clinical trial for MPS II (Hunter syndrome), and endpoints of, and dosing in, such trial; plans, timelines and expectations regarding DNL 343, including with respect to patient enrollment in, and initial safety and biomarker results from, the Phase 1b trial; plans, timelines and expectations regarding DNL788 of both Denali and Sanofi, including with respect to dosing for the Phase 2 trial in ALS and a planned Phase 2 trial in MS; plans, timelines and expectations regarding DNL593, including Phase 1/1b trial dosing and initial clinical data from such trial; plans, timeline and expectations regarding DNL758, including Sanofi's plans to initiate a Phase 2 trial in UC; plans, timelines and expectations regarding DNL919, including with respect to the clinical hold; 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 ongoing 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 Sanofi, Takeda, Biogen or any of Denali's other collaboration agreements; Denali's transition to a late stage clinical drug development company; 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 that preclinical profiles of Denali's product candidates may not translate in clinical trials; the potential for clinical trials to differ from preclinical, early clinical, preliminary or expected results; the risk of significant adverse events, toxicities or other undesirable side effects; 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, including those described in Denali's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 28, 2022 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.

Denali Therapeutics Inc.
Condensed Consolidated Statements of Operations
(Unaudited)
(In thousands, except share and per share amounts)

	Three Months Ended December 31,		Twelve Months Ended December 31,	
	2021	2020	2021	2020
Collaboration revenue:				
Collaboration revenue from customers[1]	$ 12,514	$ 316,810	$ 48,657	$ 335,561
Other collaboration revenue	—	5	4	98
Total collaboration revenue	12,514	316,815	48,661	335,659
Operating expenses:				
Research and development[2]	67,876	54,743	265,353	212,615
General and administrative	21,759	17,994	79,059	60,326
Total operating expenses	89,635	72,737	344,412	272,941
Income (loss) from operations	(77,121)	244,078	(295,751)	62,718
Interest and other income, net	1,285	1,630	4,595	9,241
Income (loss) before income taxes	(75,836)	245,708	(291,156)	71,959
Income tax benefit (expense)	575	(823)	575	(823)
Net income (loss)	$ (75,261)	$ 244,885	$ (290,581)	$ 71,136
Net income (loss) per share:				
Basic net income (loss) per share	$ (0.62)	$ 2.04	$ (2.39)	$ 0.65
Diluted net income (loss) per share	$ (0.62)	$ 1.91	$ (2.39)	$ 0.63
Weighted-average shares used in calculating:				
Basic net income (loss) per share	122,164,561	120,161,578	121,524,795	108,974,137
Diluted net income (loss) per share	122,164,561	128,297,841	121,524,795	112,703,108

(1) Includes related party collaboration revenue from customer of $1,190 and $3,736 for the quarter and year ended December 31, 2021, respectively, and $307,437 for both the quarter and year ended December 31, 2020.
(2) Includes an offset to expense from related party cost reimbursement of $1,227 and $6,499 for the quarter and year ended December 31, 2021, respectively, and $9,260 for both the quarter and year ended December 31, 2020.

Denali Therapeutics Inc.
Condensed Consolidated Balance Sheets
(Unaudited)
(In thousands)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 293,477	$ 507,144
Short-term marketable securities	571,930	962,553
Cost sharing reimbursements due from related party	1,226	5,674
Prepaid expenses and other current assets	30,601	20,284
Total current assets	897,234	1,495,655
Long-term marketable securities	425,449	32,699
Property and equipment, net	38,865	40,846
Operating lease right-of-use asset	30,743	32,618
Other non-current assets	11,871	2,462
Total assets	$ 1,404,162	$ 1,604,280
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 4,779	$ 1,071
Accrued expenses and other current liabilities	53,165	47,145
Related party contract liability, current	292,386	3,569
Contract liabilities, current	27,915	19,914
Total current liabilities	378,245	71,699
Related party contract liability, less current portion	1,295	293,849
Contract liabilities, less current portion	3,398	23,325
Operating lease liability, less current portion	58,554	64,175
Other non-current liabilities	379	701
Total liabilities	441,871	453,749
Total stockholders' equity	962,291	1,150,531
Total liabilities and stockholders' equity	$ 1,404,162	$ 1,604,280

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