# Denali Therapeutics Reports Fourth Quarter and Full Year 2022 Financial Results and Business Highlights

February 27, 2023

SOUTH SAN FRANCISCO, Calif., Feb. 27, 2023 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (Nasdaq: DNLI), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for the treatment of neurodegenerative diseases and lysosomal storage diseases, today reported financial results for the fourth quarter and year ended December 31, 2022, and provided business highlights.

“2022 was an important year for Denali, marked by transition to late-stage clinical development in our therapeutic programs for Parkinson's, MPS II, and ALS, as well as expansion of our Transport Vehicle (TV)-enabled portfolio with first-in-human studies in programs for FTD-GRN and Alzheimer’s,” said Ryan Watts, Ph.D., Denali's Chief Executive Officer. “We remain focused on progressing our broad and diversified therapeutic portfolio, further validating and expanding our TV platform, and building commercial capabilities with the ultimate goal of delivering effective medicines to people living with neurodegenerative and lysosomal storage diseases worldwide.”

**Recent Program Updates and Expected Milestones:**

**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 behavioral, cognitive and physical manifestations of MPS II (Hunter syndrome).

- In February 2023, at the WORLD*Symposium*™, Denali reported additional interim data from the open-label, single-arm Phase 1/2 study of DNL310. Over 49 weeks of DNL310 treatment in the Phase 1/2 study, positive changes across measures of exploratory clinical outcomes including VABS-II (adaptive behavior) and BSID-III (cognitive capabilities) scores and global impression scales were observed. The data also suggested that DNL310 improved hearing, as assessed by auditory brainstem response testing. Additional biomarker data out to 49 weeks continued to demonstrate that DNL310 enabled rapid and sustained normalization of CSF heparan sulfate to normal healthy levels and improvement in lysosomal function biomarkers. The DNL310 safety profile, with up to two years of treatment, remained consistent with standard of care.
- The Phase 2/3 COMPASS study continues to enroll 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.

**TAK-594/DNL593 (PTV:PGRN): Frontotemporal Dementia-Granulin (FTD-GRN)**
TAK-594/DNL593 is an investigational, Protein Transport Vehicle (PTV)-enabled, brain-penetrant progranulin (PGRN) replacement therapy. DNL593 is being co-developed with Takeda.

- In November 2022, Denali announced interim results from Part A of the Phase 1/2 study demonstrating in healthy volunteers that single doses of DNL593 resulted in substantial increases in CSF PGRN levels and were generally well tolerated, based on blinded safety analysis. Final Part A data is expected to be available in mid 2023.
- Recruitment of participants with FTD-GRN in Part B (ascending multiple doses) of the Phase 1/2 study is ongoing.

**TAK-920/DNL919 (ATV:TREM2): Alzheimer’s disease**
TAK-920/DNL919 is an investigational, Antibody Transport Vehicle (ATV)-enabled, brain-penetrant TREM2 agonist intended to improve microglial function as a potential treatment for Alzheimer’s disease. DNL919 is being co-developed with Takeda.

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

**DNL126 (ETV:SGSH): MPS IIIA (Sanfilippo syndrome Type A)**
DNL126 is an investigational, ETV-enabled, brain-penetrant N-sulfoglucosamine sulfohydrolase (SGSH) replacement therapy designed to address the behavioral, cognitive and physical manifestations of MPS IIIA (Sanfilippo syndrome Type A).

- In February 2023, Denali presented supportive preclinical data at the WORLD*Symposium*™ demonstrating that DNL126 reduced heparan sulfate in a dose-dependent manner in brain and CSF in an MPS IIIA mouse model.
- Denali anticipates submitting an investigational new drug (IND) application in the first half of 2023, with Phase 1/2 recruitment activities to begin in the second half of 2023.

**Oligonucleotide Transport Vehicle (OTV) platform**
Denali’s Oligonucleotide Transport Vehicle (OTV) platform is designed to enable peripheral administration of oligonucleotide

therapeutics, such as antisense oligonucleotides (ASOs), to address a wide range of neurodegenerative and other neurological diseases.

- In January 2023, Denali announced the selection of 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 an investigational small molecule inhibitor of LRRK2, one of the most common genetic drivers of Parkinson's disease. Targeting LRRK2 has the potential to impact the underlying biology and slow the progression of Parkinson's disease. Denali and Biogen are co-developing BIIB122.

- In October 2022, Denali and Biogen announced initiation of the global Phase 3 LIGHTHOUSE study of BIIB122 in up to 400 participants with Parkinson's disease and a confirmed LRRK2 pathogenic variant.
- Dosing is ongoing in the global Phase 2b LUMA study in up to 640 participants with early-stage Parkinson's disease.

**SAR443820/DNL788 (CNS-penetrant RIPK1 inhibitor): ALS, MS**
SAR443820/DNL788 is a CNS-penetrant, 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. Denali and Sanofi are co-developing SAR443820.

- In January 2023, Denali announced that Sanofi initiated a Phase 2 clinical trial in multiple sclerosis (MS) for which Denali received a milestone payment of $25 million.
- In November 2022, Sanofi presented Phase 1 healthy volunteer data on SAR443820 at the Annual Northeast Amyotrophic Lateral Sclerosis (NEALS) Meeting demonstrating that safety goals and target engagement goals were achieved.
- Completion of recruitment in the global Phase 2 HIMALAYA study for participants with amyotrophic lateral sclerosis (ALS) is expected by the end of 2023.

**DNL343 (eIF2B activator): ALS**
DNL343, a small molecule activator of the eukaryotic initiation factor 2B (eIF2B), is designed to inhibit the cellular integrated stress response (ISR) and thereby restore protein synthesis, disperse TDP-43 aggregates, and improve neuronal survival.

- In December 2022, at the International Symposium on ALS/MND, Denali presented results from an interim analysis of the Phase 1b study demonstrating 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. Final data from the 28-day double-blind, placebo-controlled portion of the Phase 1b study in ALS is expected to be available in mid 2023.
- In December 2022, Denali 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. The Phase 2/3 study is expected to begin in mid 2023.

**OTHER CLINICAL PROGRAMS**

**SAR443122/DNL758 (peripherally restricted RIPK1 inhibitor): CLE and UC**
SAR443122/DNL758 (eclitasertib), is a peripherally restricted, small molecule inhibitor of RIPK1. Under the collaboration agreement with Denali, Sanofi is solely responsible for the development and commercialization of peripherally restricted RIPK1 inhibitors.

- In January 2023, Denali announced that Sanofi had initiated a Phase 2 trial of SAR443122 in patients with ulcerative colitis (UC).
- Primary completion of the Phase 2 study in patients with cutaneous lupus erythematosus (CLE) is anticipated in June 2023.

**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, and other indications.

**Recent Corporate Updates:**
In October 2022, Denali raised net proceeds of approximately $296.2 million through a public offering of its common stock.

**2023 Guidance on Operating Expenses:**
Cash, cash equivalents, and marketable securities were $1.34 billion as of December 31, 2022. For the full year 2023, Denali anticipates an increase of approximately 25-30% in cash operating expenses compared to 2022, partially offset by up to $50 million from incoming cash and milestone payments from Denali's current partnerships, including $25 million received from Sanofi in January 2023 for the initiation of the Phase 2 trial of SAR443820 in patients with MS.

**Participation in Upcoming Investor Conferences:**

- Cowen 43rd Annual Health Care Conference, March 6-8
- Oppenheimer 33rd Annual Healthcare Conference, March 13-15
- 2nd Annual Needham Virtual Neuroscience Forum, March 15
- Stifel 2023 CNS Days, March 28-29
- Bank of America 2023 Health Care Conference, May 9-11
- 44th Annual Global Healthcare Conference, June 12-15

**Expected 2023 Key Milestones for Denali-Led Programs**

| Program | Milestone | Timing |
|---|---|---|
| DNL310 (ETV:IDS) | • Additional interim Phase 1/2 data at WORLD | Feb 22 – 26 |
| | • Additional Interim Phase 1/2 data at SSIEM | Aug 29 – Sept 1 |
| | • Continued recruitment of participants with MPS II in the global Phase 2/3 COMPASS study | 2023 |
| TAK-594/DNL593 (PTV:PGRN) | • Final data from Phase 1/2 Part A healthy volunteer study | Mid 2023 |
| | • Continued recruitment of participants with FTD-GRN in Part B of the Phase 1/2 study | 2023 |
| TAK-920/DNL919 (ATV:TREM2) | • Data from the Phase 1 single ascending dose study in healthy volunteers | Year-end 2023 |
| DNL126 (ETV:SGSH) | • Preclinical data at WORLD | Feb 22 – 26 |
| | • Submission of an IND application | 1H 2023 |
| | • Phase 1/2 recruitment activities | 2H 2023 |
| DNL343 (eIF2B activator) | • Final data from the 28-day double-blind, placebo-controlled portion of the Phase 1b study in ALS | Mid 2023 |
| | • Initiation of Phase 2/3 study in the HEALEY ALS Platform Trial | Mid 2023 |

**Expected 2023 Key Milestones for Partner-Led Programs**

| Program | Milestone | Strategic Partner |
|---|---|---|
| BIIB122/DNL151 (LRRK2 inhibitor) | • Continued recruitment of participants with Parkinson's disease in the Phase 2b LUMA study and the Phase 3 LIGHTHOUSE study | Biogen |
| SAR443820/DNL788 (CNS-penetrant RIPK1 inhibitor) | • Initiation of Phase 2 study in MS | Sanofi |
| | • Completion of recruitment of participants with ALS in the Phase 2 HIMALAYA study | |

| | | |
|---|---|---|
| SAR443122/DNL758 (eclitasertib) (peripherally-restricted RIPK1 inhibitor) | • Primary completion of Phase 2 CLE study | Sanofi |
| | • Continued recruitment of Phase 2 UC study | |

**Fourth Quarter and Full Year 2022 Financial Results**

Net losses were $98.7 million and $326.0 million for the quarter and year ended December 31, 2022, compared to net losses of $75.3 million and $290.6 million for quarter and year ended December 31, 2021, respectively.

Collaboration revenue was $10.3 million and $108.5 million for the quarter and year ended December 31, 2022, compared to $12.5 million and $48.7 million for the quarter and year ended December 31, 2021, respectively. The decrease in collaboration revenue of $2.2 million for the quarter ended December 31, 2022, compared to the comparative period in the prior year was primarily due to a decrease in revenue from our collaboration with Takeda due to option payments received in the prior year fourth quarter, partially offset by an increase in revenue from our collaboration with Sanofi pertaining to timing of milestone payments received in the current year fourth quarter. The increase in collaboration revenue of $59.8 million for the year ended December 31, 2022 was primarily due to the performance obligation satisfaction of the Tau program and preclinical milestone payments earned for CTA approvals of TAK-920/DNL919 and TAK-594/DNL593 under the Takeda Collaboration Agreement and increased milestone payments received under the Sanofi Collaboration Agreement, partially offset by a decrease in revenue from Biogen.

Total research and development expenses were $92.1 million and $358.7 million for the quarter and year ended December 31, 2022, compared to $67.9 million and $265.3 million for the quarter and year ended December 31, 2021, respectively. The increases of approximately $24.2 million and $93.4 million for the quarter and year ended December 31, 2022, 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 the progression of Denali's portfolio, including costs related to the progress of the ETV:IDS, PTV:PGRN and LRRK2 programs, the advancement of the TV platform, and Denali's continued overall investment in developing a broad pipeline. Net cost sharing reimbursements have decreased for the quarter and year ended December 31, 2022 as cost sharing payments owed to Biogen have increased. These net expense increases were partially offset by a decrease in ATV:TREM2 program external expenses due to the timing of clinical activities.

General and administrative expenses were $23.5 million and $90.5 million for the quarter and year ended December 31, 2022, compared to $21.8 million and $79.1 million for the quarter and year ended December 31, 2021, respectively. The increases of approximately $1.7 million and $11.4 million for the quarter and year ended December 31, 2022, respectively, were primarily attributable to an increase in personnel-related expenses, including employee compensation and stock-based compensation expenses, driven by higher headcount and equity award grants. Additionally, there were increases in facilities and other general corporate services costs including IT services and subscriptions, taxes, travel-related expenses, and consulting professional services expenses.

**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 the treatment of neurodegenerative diseases and lysosomal storage 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 expectations regarding Denali’s TV technology platform; plans, timelines, and expectations regarding DNL310, the ongoing Phase 2/3 COMPASS and Phase 1/2 studies, and the potential for the DNL310 combined data package to support registration; plans, timelines, and expectations of both Denali and Takeda regarding DNL593 and the ongoing Phase 1/2 study, including the timing and availability of final data from such trial; plans, timelines, and expectations of both Denali and Takeda regarding DNL919 and the ongoing Phase 1 study, including the timing of availability of data from such trial; plans, timelines, and expectations related to DNL126, including the expectation and timing of preclinical data and potential regulatory submissions and the planned Phase 1/2 trial; plans, timelines, and expectations regarding the advancement of OTV candidates towards clinical development; plans, timelines and expectations of both Denali and Biogen regarding DNL151, the ongoing Phase 2b LUMA study, and the ongoing Phase 3 LIGHTHOUSE study; plans, timelines and expectations regarding DNL788 of both Denali and Sanofi, including the timing and enrollment for Phase 2 trials in MS and ALS; plans, timelines and expectations regarding DNL343, including the timing and availability of data from the ongoing Phase 1b study in ALS, and timing and expectations for the planned Phase 2/3 study in ALS; plans, timeline and expectations regarding DNL758, including timing of the Phase 2 study in CLE; 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 by the 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. Information regarding additional risks and uncertainties may be found in Denali's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on February 27, 2023, 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.

**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, | |
|---|---|---|---|---|
| | **2022** | **2021** | **2022** | **2021** |
| Collaboration revenue: | | | | |
| Collaboration revenue from customers[1] | $ 10,260 | $ 12,514 | $ 105,065 | $ 48,657 |
| Other collaboration revenue | 23 | — | 3,398 | 4 |
| Total collaboration revenue | 10,283 | 12,514 | 108,463 | 48,661 |
| Operating expenses: | | | | |
| Research and development[2] | 92,111 | 67,876 | 358,732 | 265,353 |
| General and administrative | 23,516 | 21,759 | 90,475 | 79,059 |
| Total operating expenses | 115,627 | 89,635 | 449,207 | 344,412 |
| Loss from operations | (105,344) | (77,121) | (340,744) | (295,751) |
| Interest and other income, net | 6,660 | 1,285 | 14,774 | 4,595 |
| Loss before income taxes | (98,684) | (75,836) | (325,970) | (291,156) |
| Income tax benefit (expense) | 6 | 575 | (21) | 575 |
| Net loss | $ (98,678) | $ (75,261) | $ (325,991) | $ (290,581) |
| Net loss per share, basic and diluted | $ (0.75) | $ (0.62) | $ (2.60) | $ (2.39) |
| Weighted average number of shares outstanding, basic and diluted | 132,877,411 | 122,164,561 | 125,530,703 | 121,524,795 |

(1) Includes related-party collaboration revenue from a customer of $0.3 million and $3.2 million for the quarter and year ended December 31, 2022, respectively, and $1.2 million and $3.7 million for the quarter and year ended December 31, 2021, respectively.

(2) Includes expense for cost sharing payments due to a related party of $4.4 million and $8.2 million for the quarter and year ended December 31, 2022, respectively, and an offset to expense from related-party cost sharing reimbursements of $1.2 million and $6.5 million for the quarter and year ended December 31, 2021, respectively.

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

| | December 31, 2022 | December 31, 2021 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |

| | | |
|---|---|---|
| Cash and cash equivalents | $ 218,044 | $ 293,477 |
| Short-term marketable securities | 1,118,171 | 571,930 |
| Cost sharing reimbursements due from related party | — | 1,226 |
| Prepaid expenses and other current assets | 36,104 | 30,601 |
| Total current assets | 1,372,319 | 897,234 |
| Long-term marketable securities | — | 425,449 |
| Property and equipment, net | 44,087 | 38,865 |
| Operating lease right-of-use assets | 30,437 | 30,743 |
| Other non-current assets | 13,399 | 11,871 |
| Total assets | $ 1,460,242 | $ 1,404,162 |
| **Liabilities and stockholders' equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 2,790 | $ 4,779 |
| Cost sharing payments due to related party | 4,388 | — |
| Accrued expenses and other current liabilities | 66,691 | 53,165 |
| Related-party contract liability, current | 290,053 | 292,386 |
| Contract liabilities, current | — | 27,915 |
| Total current liabilities | 363,922 | 378,245 |
| Related-party contract liability, less current portion | 479 | 1,295 |
| Contract liabilities, less current portion | — | 3,398 |
| Operating lease liabilities, less current portion | 53,032 | 58,554 |
| Other non-current liabilities | 379 | 379 |
| Total liabilities | 417,812 | 441,871 |
| Total stockholders' equity | 1,042,430 | 962,291 |
| Total liabilities and stockholders’ equity | $ 1,460,242 | $ 1,404,162 |

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