Denali Therapeutics Reports Second Quarter 2023 Financial Results and Business Highlights

August 8, 2023 8:01 PM PDT

SOUTH SAN FRANCISCO, Calif., Aug. 08, 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 second quarter ended June 30, 2023, and provided business highlights.

“In the second quarter, we shared exciting new data demonstrating robust reduction in NfL in the Phase 1/2 MPS II trial with DNL310 (ETV:IDS) and target engagement with DNL343 (eIF2B activator) in the Phase 1b study in ALS patients, which support ongoing late-stage studies for those programs,” said Ryan Watts, Ph.D., Chief Executive Officer at Denali. “On our partnered programs, we and Takeda have made a strategic decision to discontinue development of TAK-920/DNL919 (ATV:TREM2) in Alzheimer’s disease based on data from the Phase 1 study and the rapidly evolving treatment landscape. We will continue to explore back-up molecules, including potential combination therapies in Alzheimer’s disease. Separately, Biogen exercised their option to our ATV-amyloid-beta program for Alzheimer’s disease. Also with Biogen, we made revisions to the BIIB122 (LRRK2 inhibitor) clinical development plan intended to increase efficiency by focusing on one study in Parkinson’s disease. These strategic decisions reflect our data-driven approach to resource optimization and portfolio prioritization as we focus on late-stage programs and commercial readiness.”

Second Quarter and Recent Program Updates:

TV-ENABLED PROGRAMS

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

DNL310 is an investigational, intravenously administered, Enzyme Transport Vehicle (ETV)-enabled, iduronate-2-sulfatase (IDS) replacement therapy designed to cross the BBB and address the behavioral, cognitive, and physical manifestations of MPS II (Hunter syndrome).

- In June, Denali announced new interim results demonstrating a robust reduction in neurofilament light (NfL), a marker of neuroaxonal damage, from the ongoing open-label, single-arm Phase 1/2 study of DNL310 in children with MPS II. A decline in serum NfL levels was observed after six months of treatment with DNL310, reaching a statistically significant reduction of approximately 40% ($p < 0.001$) at Week 61 and approximately 64% ($p < 0.001$) after two years of treatment with DNL310 compared to baseline. The previously reported robust reduction and normalization of heparan sulfate levels in cerebrospinal fluid (CSF), and now the downstream reduction in NfL after treatment, are consistent with positive changes in clinical outcomes measures that Denali has previously reported from interim analyses of the Phase 1/2 study.

- In June, Denali announced that the U.S. Food and Drug Administration (FDA) had recently recommended to Denali the assessment of NfL as an exploratory endpoint to evaluate its potential as a possible biomarker to assess diagnostic, prognostic, or therapeutic response in subjects with neuronopathic MPS II. Denali intends to share the new NfL data with the FDA at an upcoming meeting as part of the ongoing dialogue related to the DNL310 development program.

- Additional interim data from the Phase 1/2 study of DNL310 will be highlighted in an oral presentation at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium 2023 in Jerusalem, Israel, August 29 – September 1, 2023.

- Recruitment of participants with MPS II, with and without neuronopathic disease, in the global Phase 2/3 COMPASS study is ongoing.

TAK-594/DNL593 (PTV:PGRN): Frontotemporal Dementia-Granulin (FTD-GRN)

DNL593 is an investigational, intravenously administered, Protein Transport Vehicle (PTV)-enabled progranulin (PGRN) replacement therapy designed to restore normal levels of PGRN in the brain without interfering with normal PGRN transport and processing. DNL593 is being co-developed with Takeda.

- In July, Denali presented additional healthy volunteer data from Part A of the Phase 1/2 study at the Alzheimer's Association International Conference, which continued to demonstrate that single doses of DNL593 resulted in substantial increases in CSF PGRN levels and were generally well tolerated.

- Recruitment of participants with symptomatic FTD-GRN loss of function mutations 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, TREM2 agonist intended to improve microglial function as a potential treatment for Alzheimer's disease, which is being co-developed with Takeda.

- Denali announced that, in agreement with Takeda, the companies will discontinue clinical development of DNL919 in Alzheimer's disease. This is a strategic decision based on the totality of clinical data emerging from the single ascending dose Phase 1 study of DNL919 in healthy volunteers and in consideration of the rapidly evolving treatment landscape for Alzheimer's disease whereby an understanding of drug combinations with newly approved therapies will be important.

- A preliminary analysis of Phase 1 data indicates robust target engagement and effects on microglial biomarkers (e.g., CSF1R, SPP1, IL1RA, IP10, MIP1b, MCP-1), which were consistent with preclinical studies that demonstrate that ATV:TREM2 induces robust changes to a responsive microglial cell state (van Lengerich B, et al. Nat Neurosci. 2023).

- In the Phase 1 study, DNL919 was clinically well tolerated at doses with demonstrated changes in CSF biomarkers and there were no serious adverse events or severe treatment emergent adverse events; however, safety signals of moderate, reversible hematologic effects were observed at the highest dose tested, suggesting a narrow therapeutic window for the Alzheimer's disease patient population. The Phase 1 safety findings are believed to be specific to properties of DNL919 and TREM2 biology.

- Denali and Takeda will focus research efforts on back-up molecules in preclinical development, including exploration of potential combination therapy given recent new drug approvals in Alzheimer's disease.

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

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

- Today, Denali announced that the Investigational New Drug (IND) application for DNL126 in MPS IIIA has been cleared, and plans remain on track to initiate recruiting activities for the Phase 1/2 study in the second half of 2023.

Oligonucleotide Transport Vehicle (OTV) platform

Denali's 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. Denali has submitted a manuscript for publication, which can be found on bioRxiv here. Denali has selected five ASO targets for further development and is focused on advancing two OTV candidates towards clinical development.

Antibody Transport Vehicle Amyloid beta (ATV-amyloid-beta) program

ATV-amyloid-beta is an investigational, ATV-enabled anti-amyloid-beta therapy designed to increase brain exposure and target engagement of antibody therapeutics directed against amyloid-beta, which may enable improved plaque clearance and/or reduced amyloid-related imaging abnormalities (ARIA). Accumulation of amyloid-beta plaque in the brain is a defining feature of Alzheimer's disease. Biogen exercised its option to license Denali's ATV-amyloid-beta program and is responsible for all development and commercial activities and associated expenses.

SMALL MOLECULE PROGRAMS

BIIB122/DNL151 (LRRK2 Inhibitor): Parkinson's disease

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 June, Denali in conjunction with Biogen, and based on review of portfolio timelines and resource prioritization, announced plans to revise the clinical development program for BIIB122/DNL151. Prior to the planned revisions, the BIIB122 clinical development program encompassed two global late-stage clinical trials: the Phase 2b LUMA study in participants with early-stage Parkinson's disease, which commenced in May 2022; and the Phase 3 LIGHTHOUSE study in participants with Parkinson's disease related to LRRK2 mutations, which commenced in September 2022. In consideration of the LIGHTHOUSE study's complexity, including the long timeline with anticipated study completion in 2031, Biogen and Denali plan to refocus their efforts to enable a timely readout on efficacy in idiopathic early-stage Parkinson's disease while gaining further clinical data in Parkinson's disease with and without a LRRK2 mutation. The planned revisions to the BIIB122 clinical development program are not based on any safety or efficacy data from studies of BIIB122. Biogen and Denali will modify the LUMA study's enrollment criteria to allow for inclusion of eligible participants with Parkinson's disease and a confirmed pathogenic variant of LRRK2, in addition to continuing to enroll eligible participants with idiopathic

early-stage Parkinson's disease. Collectively, data from the LUMA study will inform next steps for the development of BIIB122 in Parkinson's disease.

SAR443820/DNL788 (CNS-Penetrant RIPK1 Inhibitor): ALS, MS

SAR443820/DNL788 is an investigational, CNS-penetrant, small molecule inhibitor of RIPK1, a critical signaling protein in a canonical inflammatory and cell death pathway. Increased RIPK1 activity in the CNS is hypothesized to drive neuroinflammation and cell necroptosis and to contribute to neurodegeneration. Denali and Sanofi are co-developing SAR443820. Sanofi is conducting the global Phase 2 HIMALAYA study for participants with amyotrophic lateral sclerosis (ALS) and a Phase 2 clinical trial for participants with multiple sclerosis (MS).

- In July, Sanofi completed enrollment in the Phase 2 HIMALAYA study; primary completion of the study is estimated to be February 2024.

DNL343 (eIF2B Activator): ALS

DNL343 is an investigational small molecule activator of the eukaryotic initiation factor 2B (eIF2B) designed to inhibit the cellular integrated stress response (ISR) and prevent or slow disease progression by interfering with stress granule formation and TDP-43 aggregation, which is a hallmark pathology present in virtually all individuals with ALS. Previously announced results of a Phase 1b study in participants with ALS demonstrated that once-daily oral dosing with DNL343 for 28 days was generally well-tolerated and was associated with extensive distribution in the cerebrospinal fluid as well as robust inhibition of ISR biomarkers.

- In May, the first patient was dosed with DNL343 in the Phase 2/3 HEALEY ALS Platform Trial.

OTHER CLINICAL PROGRAMS

SAR443122/DNL758 (Peripheral RIPK1 Inhibitor): CLE and UC

SAR443122/DNL758 (eclitasertib), is an investigational, peripherally restricted, small molecule inhibitor of RIPK1. Sanofi is solely responsible for the development and commercialization of peripherally restricted RIPK1 inhibitors.

- In June, Sanofi completed a Phase 2 study of DNL758 in patients with cutaneous lupus erythematosus (CLE); data analysis is ongoing.

- Sanofi is conducting a Phase 2 trial of SAR443122 in patients with ulcerative colitis (UC).

DISCOVERY PROGRAMS

Denali continues to selectively advance a broad preclinical portfolio including programs enabled by the Enzyme Transport Vehicle, the Antibody Transport Vehicle, 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.

Participation in Upcoming Investor Conferences:

- Morgan Stanley 21st Annual Global Healthcare Conference, September 11-13

- H.C. Wainwright 25th Annual Global Investment Conference, September 11-13

Second Quarter 2023 Financial Results

For the three months ended June 30, 2023, Denali reported net income of $183.4 million compared to a net loss of $58.8 million for the three months ended June 30, 2022.

Collaboration revenue was $294.1 million and $52.5 million for the three months ended June 30, 2023 and 2022, respectively. The increase in collaboration revenue of $241.6 million for the three months ended June 30, 2023, compared to the comparative period in the prior year was primarily due to an increase in revenue under the Biogen Collaboration Agreement of $293.6 million as a result of Biogen exercising their option to license our ATV:Abeta program, including $288.9 million previously recognized as a related-party contract liability. These increases are partially offset by a decrease of $40.0 million in revenue from our collaboration with Sanofi and a decrease of $12.0 million in revenue earned under the Takeda Collaboration Agreement in the three months ended June 30, 2023 compared to June 30, 2022, both due to the timing of underlying activities and milestone triggers under the collaboration agreements.

Total research and development expenses were $97.5 million and $92.7 million for the three months ended June 30, 2023 and 2022, respectively. The increase of approximately $4.8 million for the three months ended June 30, 2023 compared to the comparative period in the prior year was primarily attributable to increases in ETV:IDS and eIF2B program external expenses reflecting the continued progress of these programs in clinical trials during 2023; an increase in other unallocated research and development expenses primarily due to increased facility costs, including utilities and building repairs and maintenance; and an increase in personnel-related expenses, including stock-based compensation, mainly driven by higher headcount and equity award grants. Further, net cost sharing reimbursements from collaboration partners decreased as cost sharing payments owed to Biogen

increased. These net expense increases were partially offset by decreases in LRRK2 program external expenses due to the transition of LRRK2 clinical activities to Biogen, TV platform and other program external expenses, and PTV:PGRN program external expenses due to the timing of significant external research and manufacturing related activities period over period.

General and administrative expenses were $26.1 million and $21.2 million for the three months ended June 30, 2023 and 2022, respectively. The increase of approximately $4.9 million for the three months ended June 30, 2023 compared to the comparative period in the prior year was 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, consulting, and other professional services costs.

Cash, cash equivalents, and marketable securities were approximately $1.19 billion as of June 30, 2023.

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, including the Enzyme Transport Vehicle (ETV), Antibody Transport Vehicle (ATV) and Oligonucleotide Transport Vehicle (OTV); statements made by Denali's Chief Executive Officer; plans, timelines, and expectations regarding DNL310 and the ongoing Phase 2/3 COMPASS and Phase 1/2 studies, including the continued recruitment of participants for the Phase 2/3 COMPASS study and the timing and availability of data for the Phase 1/2 study; plans, timelines, and expectations of both Denali and Takeda regarding DNL593 and the ongoing Phase 1/2 study, including the recruitment of patients for the Part B study; plans and expectations related to the therapeutic potential of DNL919 and any back-up molecules in preclinical development; plans, timelines, and expectations related to DNL126, including timing for initiation of recruitment for the Phase 1/2 study; plans, timelines, and expectations regarding the advancement of OTV candidates towards clinical development; plans, timelines, and expectations of both Denali and Biogen regarding the development of Denali's ATV:Abeta for the treatment of Alzheimer's disease; plans, timelines, and expectations of both Denali and Biogen regarding DNL151, the enrollment and timing and availability of data from the ongoing Phase 2b LUMA study; plans, timelines, and expectations regarding DNL788 of both Denali and Sanofi; plans, timelines, and expectations regarding DNL343, including plans for the Phase 2/3 HEALEY ALS Platform Trial; plans, timelines, and expectations regarding DNL758, including the availability of data from the completed Phase 2 study in patients with CLE and the ongoing Phase 2 study in patients with UC; and plans and expectations for Denali's preclinical programs. 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 adverse economic conditions; 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, or 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; 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; and other risks and uncertainties, including those described in Denali's most recent Annual and Quarterly Reports on Forms 10-K and 10-Q filed with the Securities and Exchange Commission (SEC) on February 27, 2023 and May 8, 2023, 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.

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

	Three Months Ended June 30,	Six Months Ended June 30,

	2023	2022	2023	2022
Collaboration revenue:				
Collaboration revenue from customers[1]	$ 294,123	$ 52,480	$ 329,264	$ 94,621
Total collaboration revenue	294,123	52,480	329,264	94,621
Operating expenses:				
Research and development[2]	97,520	92,737	226,336	178,835
General and administrative	26,120	21,159	53,260	43,700
Total operating expenses	123,640	113,896	279,596	222,535
Income (loss) from operations	170,483	(61,416)	49,668	(127,914)
Interest and other income, net	12,900	2,649	23,934	3,927
Income (loss) before income taxes	183,383	(58,767)	73,602	(123,987)
Income tax expense	—	(27)	—	(27)
Net income (loss)	$ 183,383	$ (58,794)	$ 73,602	$ (124,014)
Net income (loss) per share:				
Net income (loss) per share, basic	$ 1.34	$ (0.48)	$ 0.54	$ (1.01)
Net income (loss) per share, diluted	$ 1.30	$ (0.48)	$ 0.52	$ (1.01)
Weighted-average shares used in calculating:				
Weighted average number of shares outstanding, basic	137,047,227	123,008,558	136,787,321	122,842,171
Weighted average number of shares outstanding, diluted	140,930,625	123,008,558	140,550,226	122,842,171

(1) Includes related-party collaboration revenue from customers of $294.1 million and $294.3 million for the three and six months ended June 30, 2023, respectively, and $0.5 million and $2.7 million for the three and six months ended June 30, 2022, respectively.

(2) Includes expenses for cost sharing payments due to a related party of $7.0 million and $11.1 million for the three and six months ended June 30, 2023, respectively, an offset to expense from related-party cost sharing reimbursements of $0.4 million for the three months ended June 30, 2022, and expense for cost sharing payments due to a related party of $2.4 million for the six months ended June 30, 2022.

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

	June 30, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 131,973	$ 218,044
Short-term marketable securities	1,059,014	1,118,171
Prepaid expenses and other current assets	33,075	36,104
Total current assets	1,224,062	1,372,319
Property and equipment, net	39,821	44,087
Operating lease right-of-use assets	27,417	30,437
Other non-current assets	14,434	13,399
Total assets	$ 1,305,734	$ 1,460,242
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 8,520	$ 2,790
Cost sharing payments due to related party	6,976	4,388
Accrued clinical and other research & development costs	15,120	16,297
Accrued manufacturing costs	17,263	22,307
Other accrued costs and current liabilities	3,603	3,682
Accrued compensation	10,256	17,087
Operating lease liabilities, current	6,774	7,318
Related-party contract liability, current	845	290,053
Total current liabilities	69,357	363,922

Related-party contract liability, less current portion	422	479
Operating lease liabilities, less current portion	48,751	53,032
Other non-current liabilities	379	379
Total liabilities	118,909	417,812
Total stockholders' equity	1,186,825	1,042,430
Total liabilities and stockholders’ equity	$ 1,305,734	$ 1,460,242

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Source: Denali Therapeutics Inc.