Denali Therapeutics Announces Key Anticipated 2024 Milestones and Priorities to Further Advance Its Therapeutics Portfolio for Neurodegeneration and Lysosomal Storage Diseases

January 8, 2024

- Complete enrollment in Denali-led, late-stage programs for MPS II and ALS, and establish commercial readiness
- Advance broad clinical-stage portfolio of seven therapeutic product candidates across neurodegeneration (ALS, Parkinson's disease, MS, FTD-GRN), lysosomal storage disease (MPS II, MPS IIIA), and inflammatory disease (UC)
- Advance OTV:MAPT targeting tau for Alzheimer's disease and OTV:SNCA targeting alpha-synuclein for Parkinson's disease in IND-enabling studies
- Prioritize preclinical portfolio with focus on Transport Vehicle-enabled biotherapeutics

SOUTH SAN FRANCISCO, Calif., Jan. 08, 2024 (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 announced program progress and expected milestones for 2024, which Chief Executive Officer, Ryan Watts, Ph.D., will highlight during a corporate presentation at the 42nd Annual J.P. Morgan Healthcare Conference on Tuesday, January 9th, at 10:30 a.m. Pacific Time.

"In 2024, we expect enrollment to be completed in our late-stage clinical trials for MPS II and ALS, and we are establishing commercial readiness," said Ryan Watts, Ph.D., Chief Executive Officer of Denali. "In addition, we are excited to announce initiation of clinical development for our second Enzyme Transport Vehicle (TV)-enabled program, DNL126 in MPS IIIA, and that our first two Oligonucleotide TV-enabled programs are in IND-enabling studies targeting tau in Alzheimer's disease (OTV:MAPT) and alpha-synuclein in Parkinson's disease (OTV:SNCA). Based on clinical validation and momentum with the TV platform, we have prioritized advancing additional TV programs for common neurodegenerative diseases."

Denali's 2024 Outlook

Expected progress and key milestones in 2024 across Denali's therapeutic portfolio are summarized below.

LATE-STAGE AND MID-STAGE CLINICAL PROGRAMS

Tividenofusp alfa (DNL310): MPS II (Hunter syndrome)

Tividenofusp alfa (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).

Interim Phase 1/2 study data up to two years of treatment have demonstrated that once weekly intravenous dosing with DNL310 was generally well-tolerated and led to rapid and sustained normalization of cerebral spinal fluid (CSF) heparan sulfate to normal healthy levels, improvement in lysosomal function biomarkers, and robust and statistically significant reduction of neurofilament light (NfL), a marker of neuronal damage. In addition, positive clinical outcome changes in adaptive behavior, cognition, and auditory function were observed.

The global Phase 2/3 COMPASS study continues to recruit up to 54 participants with neuronopathic and non-neuronopathic MPS II. Upon completion of the ongoing Phase 1/2 study, and together with data from COMPASS, this combined data package is intended to support registration.

2024 expected progress and milestones:

- Complete enrollment of global Phase 2/3 COMPASS study in MPS II
- Presentation of additional interim Phase 1/2 data at WORLDSymposium™ (February 4-9) and at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium (September 3-6)

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. Recruitment is ongoing in Regimen G (DNL343) of the Phase 2/3 HEALEY ALS Platform Trial.

2024 expected progress and milestones:

- Complete enrollment of participants in Regimen G (DNL343) in Phase 2/3 HEALEY ALS Platform Trial

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 has completed enrollment of two Phase 2 studies: 305 participants have enrolled in the HIMALAYA ALS study and 174 participants have enrolled in the K2 multiple sclerosis (MS) study.

2024 expected progress and milestones:

- Sanofi to announce topline results from the Phase 2 HIMALAYA study in ALS in the first half of 2024
- Continue K2 Phase 2 study in MS

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. Biogen is conducting the global Phase 2b LUMA study of BIIB122 in early-stage Parkinson's disease with and without LRRK2 mutations.

2024 expected progress and milestones:

- Continue Phase 2b LUMA study in early-stage Parkinson's disease

Eclitasertib (SAR443122/DNL758) (Peripheral RIPK1 Inhibitor): Ulcerative colitis (UC)

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

2024 expected progress and milestones:

- Continue Phase 2 UC study

EARLY-STAGE CLINICAL AND PRECLINICAL PROGRAMS

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. Results from Part A of a Phase 1/2 study (n=38) demonstrated that single doses of DNL593 were generally well-tolerated in healthy subjects and resulted in substantial increases in CSF PGRN levels. These data suggest brain delivery of DNL593 was achieved and has the potential to address PGRN deficiency in FTD-GRN.

Denali today also announced that enrollment and dosing have been voluntarily paused in Part B (n=9 dosed to date) of the DNL593 Phase 1/2 study in participants with FTD-GRN to implement protocol modifications. The pause is based on infusion-related reactions (IRRs) reported in two study participants, one Grade 2 and one Grade 3 in severity and both deemed serious adverse events. Both study participants' IRRs resolved with infusion discontinuation and standard treatment measures within the same day. DNL593 has been otherwise well-tolerated in the study, with all other adverse events reported as mild in severity. The protocol modification will allow for premedication and other measures aimed at reducing the risk of IRRs.

2024 expected progress and milestones:

- Continue Part B of the Phase 1/2 study in FTD-GRN

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). Recruiting activities are ongoing for the Phase 1/2 study of DNL126 in MPS IIIA.

2024 expected progress and milestones:

- Biomarker proof of concept and safety data from the Phase 1/2 study by the end of 2024

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 today announced that OTV:MAPT targeting tau for Alzheimer's disease and OTV:SNCA targeting alpha-synuclein for Parkinson's disease are the first programs in the Investigational New Drug (IND)-enabling stage of development.

2024 expected progress and milestones:

- IND-enabling studies with OTV:MAPT and OTV:SNCA

Antibody Transport Vehicle Amyloid beta (ATV:Abeta) program

ATV:Abeta 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 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:Abeta program and is responsible for all development and commercial activities and associated expenses.

2024 expected progress and milestones:

- IND-enabling studies

DISCOVERY PROGRAMS

Denali continues to use deep scientific expertise in neurodegeneration biology and the blood-brain barrier to discover and develop medicines and platforms with the focus on programs enabled by the Transport Vehicle and targeting common neurodegenerative disease, including Alzheimer's and Parkinson's, and lysosomal storage diseases.

CORPORATE UPDATES

Based on clinical validation and prioritization of Denali's TV-enabled platforms for brain delivery of large molecules, Denali today also announced its intention to spin out its preclinical small molecule portfolio with the formation of a new company ("NewCo"), which will be independently funded. A team of proven small molecule CNS drug developers with a track record of invention at Denali will assume leadership of the NewCo. Denali will maintain ownership of and continue to advance its current portfolio of clinical stage small molecule programs.

Cash, cash equivalents, and marketable securities were approximately $1.12 billion as of September 30, 2023. Denali anticipates its operating expenses in 2024 will be less than or equal to those in 2023 based on prioritization of its portfolio, thereby extending the company's cash runway into 2027.

Expected 2024 Key Milestones for Denali-Led Programs

PROGRAM	MILESTONE	TIMING
DNL310 (ETV:IDS)	Additional long-term Phase 1/2 data at WORLD	Feb 4-9
	Additional long-term Phase 1/2 data at SSIEM	Sept 3-6
	Complete enrollment of global Phase 2/3 COMPASS study in MPS II	2024
DNL593 (PTV:PGRN)	Continue Part B of Phase 1/2 study in FTD-GRN	2024
DNL126 (ETV:SGSH)	Preclinical data at WORLD	Feb 4-9
	Initiate dosing in Phase 1/2	Early 2024
	Biomarker proof of concept and safety data from Phase1/2 study in MPS IIIA	Late 2024
DNL343 (eIF2B activator)	Complete enrollment of Regimen G in Phase 2/3 HEALEY ALS Platform Trial	2024
OTV:MAPT	IND enabling studies	2024
OTV:SNCA	IND enabling studies	2024

Expected 2024 Key Milestones for Partner-Led Programs

PROGRAM	MILESTONE	STRATEGIC PARTNER
BIIB122/DNL151 (LRRK2 inhibitor)	Continue Phase 2b LUMA study in early-stage PD	Biogen
ATV:Abeta	IND enabling studies	Biogen
SAR443820/DNL788 (CNS-penetrant RIPK1 inhibitor)	Topline results of the Phase 2 HIMALAYA study in ALS (1H 2024)	Sanofi
	Continue Phase 2 K2 study in MS	
SAR443122/DNL758 (Peripherally-restricted RIPK1 inhibitor)	Continue Phase 2 UC study	Sanofi

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://investors.denalitherapeutics.com/events. An archived replay of the presentation will be available for approximately 30 days following the event.

About Denali's Transport Vehicle 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 receptors, which are expressed at the blood-brain barrier and 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 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 with respect to enrollment and the timing and availability of data; plans, timelines, and expectations of both Denali and Takeda regarding DNL593 and the ongoing Phase 1/2 study, including the modification of the study protocol and impact on the occurrence of IRRs; plans, timelines, and expectations related to DNL126, including the Phase 1/2 study, including the timing and availability of data; plans, timelines, and expectations regarding Denali's OTV platform and related programs, including the publication of manuscripts, the advancement of candidates towards clinical development, and the potential for registration; plans, timelines, and expectations of both Denali and Biogen regarding the ATV:Abeta program and its registrational potential; plans, timelines, and expectations of both Denali and Biogen regarding DNL151 and the ongoing Phase 2b LUMA study; plans, timelines, and expectations of both Denali and Sanofi regarding DNL788 and the ongoing Phase 2 HIMALAYA study in ALS and Phase 2 study in MS, including with respect to the timing and availability of data; plans, timelines, and expectations regarding DNL343, including enrollment in Regimen G of the Phase 2/3 HEALEY ALS Platform Trial; plans, timelines, and expectations regarding DNL758, including the ongoing Phase 2 study in patients with UC; the creation, funding, and leadership of NewCo; Denali's anticipated operating expenses; 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 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 November 6, 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.

Investor and Media Contact:

Laura Hansen, Ph.D.
Vice President, Investor Relations
hansen@dnli.com

Source: Denali Therapeutics Inc.