Denali Therapeutics Announces Initiation of Phase 1/2 Clinical Trial of DNL593 (PTV:PGRN) for Frontotemporal Dementia-Granulin (FTD-GRN)

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SOUTH SAN FRANCISCO, Calif., March 09, 2022 (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 neurodegenerative diseases, today announced that dosing has begun in a Phase 1/2 clinical trial of DNL593 (PTV:PGRN) for the potential treatment of frontotemporal dementia (FTD) caused by mutations in the granulin gene (*GRN*). Pending initial clinical data from the Phase 1 healthy volunteer portion of the clinical trial, Denali expects to begin dosing individuals with FTD-GRN in the second half of 2022. Denali and Takeda have a strategic collaboration to co-develop and co-commercialize DNL593.

FTD-GRN is characterized by progranulin (PGRN) deficiency in the brain. DNL593 is an investigational brain-penetrant, recombinant PGRN replacement therapy enabled by Denali's Protein Transport Vehicle (PTV:PGRN). The therapeutic goal of DNL593 is to slow or prevent progression of FTD-GRN by increasing intracellular and extracellular levels of functional PGRN.

"Denali has a diverse portfolio of therapeutic candidates to address neurodegenerative and lysosomal diseases, and DNL593 is our second Transport Vehicle (TV) technology-enabled program to enter clinical development," said Carole Ho, M.D., Denali's Chief Medical Officer. "Initiation of this Phase 1/2 trial is an important development milestone for the program, and we look forward to continued collaboration with Takeda and the FTD community in our unified purpose to develop DNL593 as a treatment option for people and families living with FTD-GRN."

"The progression of the DNL593 program into the clinic underscores the potential for Denali's Protein Transport Vehicle technology to address one of the major challenges we face in neuroscience drug development, namely the ability to effectively deliver drugs to the central nervous system. For DNL593, this means delivering what we believe to be therapeutic levels of recombinant progranulin to the brain and into neurons and glial support cells," said Sarah Sheikh, BM BCh, MSc, MRCP, Head, Neuroscience Therapeutic Area Unit at Takeda. "Through our collaboration with Denali, we have an opportunity to bring transformative treatments for people living with devastating neurological disorders such as FTD-GRN."

The Phase 1/2 clinical trial of DNL593 is a three-part (Parts A-C) multicenter, randomized, double-blind, placebo-controlled clinical trial exploring safety, pharmacokinetics and pharmacodynamics of DNL593 in healthy volunteers and patients with FTD-GRN. Dosing has begun in Part A, which is a single ascending dose study in healthy volunteers. Part B is a multiple dose, 25-week study in participants with FTD-GRN. Part C is an 18-month open label extension of participants with FTD-GRN who participated in Part B. More information about the Phase 1/2 clinical trial of DNL593 (study number NCT05262023) can be found here on the ClinicalTrials.gov website.

About Frontotemporal Dementia (FTD)

FTD is the most common form of dementia in people under 60 years of age. While the progression of symptoms varies by individual, FTD brings an inevitable decline in function together with changes in personality and social behaviors, and sometimes language and/or motor dysfunction. Mutations in the granulin (*GRN*) gene, which encodes the progranulin (PGRN) protein, generally result in reduced levels of PGRN and are amongst the most common genetic causes of FTD. There are currently no approved medicines to stop or slow the progression of FTD or FTD-GRN.

About DNL593 (PTV:PGRN)

DNL593 is an investigational, intravenously administered, brain-penetrant progranulin (PGRN) replacement therapy enabled by Denali's Protein Transport Vehicle (PTV) technology. PGRN is known to promote lysosomal function, in addition to having neurotrophic and anti-inflammatory effects. Data from *in vitro* and *in vivo* models providing preclinical proof of concept for DNL593 were published in the September 2, 2021, issue of the scientific journal *Cell*. The studies demonstrated that DNL593 enhanced brain uptake of peripherally administered PGRN by multiple cell types in the brain, including neurons and microglia, and improved lysosomal function. In addition, DNL593 rescued both neurodegeneration and microglial dysfunction in PGRN-deficient mice. These preclinical data support the potential for DNL593 to increase PGRN levels in the brain and impact disease progression in individuals with FTD-GRN.

Denali and Takeda are collaborating to co-develop and co-commercialize DNL593. Denali may receive future milestone payments from Takeda upon achievement of certain clinical and regulatory milestone events as well as certain sales-based milestones. Subject to the terms of the collaboration agreement, Denali will share the development and commercialization costs equally with Takeda, and, if applicable, profits on a worldwide basis.

DNL593 is an investigational therapeutic that has not been approved by any regulatory authority for any commercial use.

About Denali's TV Platform

The blood-brain barrier (BBB) is essential in maintaining the brain's microenvironment and protecting it from harmful substances and pathogens circulating in the bloodstream. Historically, the BBB has posed significant challenges to drug development for diseases of the central nervous system (CNS) by preventing most drugs from reaching the brain in therapeutically relevant concentrations. Denali's Transport Vehicle (TV) platform is a proprietary technology designed to effectively deliver large therapeutic molecules such as antibodies, enzymes, proteins, and oligonucleotides across the BBB after intravenous administration. The TV technology is based on engineered Fc fragments that bind to specific natural transport receptors, such as transferrin receptor, which are expressed at the BBB and deliver TV and its therapeutic cargo to the brain through receptor-mediated transcytosis. In animal models, antibodies and enzymes enabled by the TV 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 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 plans, timelines and expectations related to DNL593 and the DNL593 ongoing Phase 1/2 study, including the results of initial clinical data from the Phase 1 healthy volunteer portion of the clinical trial and the timing and expectation of dosing individuals with FTD-GRN in the second half of 2022, expectations regarding Denali's TV technology platform including its Protein Transport Vehicle (PTV) technology, the therapeutic and commercial potential of DNL593 and Denali's TV platform, Denali's progress, business plans, business strategy, product candidates, planned preclinical studies and clinical trials and expected milestones and associated payments, and statements made by Denali's Chief Medical Officer and Takeda's Head of the Neuroscience Therapeutic Area Unit. 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: Denali's early stages of clinical drug development; Denali's ability to complete the development and, if approved, commercialization of DNL593 on expected timelines; Denali's ability to initiate and enroll patients in the Phase 1/2 study of DNL593 and other future clinical trials; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; the potential for clinical trial results of DNL593 to differ from preclinical, early clinical, preliminary or expected results; Denali's ability to continue dose escalation in the Phase 1/2 study of DNL593; the risk of significant adverse events, toxicities or other undesirable side effects related to DNL593; the risk that results from early clinical biomarker studies will not translate to clinical benefit in late clinical studies; the risk that DNL593 may not receive regulatory approval for FTD-GRN necessary to be commercialized; 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 DNL593; implementation of Denali's strategic plans for its business, product candidates and blood-brain barrier platform technology, including DNL593; 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 additional risks and uncertainties may be found in Denali's 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. 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.

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