# Denali Therapeutics Announces Phase 1/2 Study Single Dose Healthy Volunteer Data with TAK-594/DNL593 (PTV:PGRN) and Progression to Enrolling Participants with FTD-GRN

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- Interim results from Part A in healthy volunteers demonstrated dose-dependent increases in CSF progranulin levels, consistent with robust brain delivery of DNL593
- Single doses of DNL593 were generally well tolerated
- Data support progression to enrolling participants with FTD-GRN in Part B of the Phase 1/2 study

SOUTH SAN FRANCISCO, Calif., Nov. 01, 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 for neurodegenerative diseases and lysosomal storage disorders, today announced interim results from Part A of a Phase 1/2 study evaluating TAK-594/DNL593 (PTV:PGRN) in healthy subjects. Progranulin (PGRN) levels measured in cerebrospinal fluid (CSF) increased in a dose-dependent manner compared to baseline and placebo, consistent with brain delivery of DNL593 and exceeding levels believed to be necessary to rescue deficits associated with progranulin deficiency, based on preclinical models.[1] Single doses of DNL593 were generally well tolerated, based on blinded safety analysis. These data support dosing in participants with frontotemporal dementia and a mutation in the granulin gene (FTD-GRN) in Part B of the study. DNL593 is an investigational, brain-penetrant progranulin replacement therapy being co-developed by Denali and Takeda. These data were presented at the FTD Prevention Initiative meeting in Paris, France. A copy of the presentation is available on Denali's website on the Investor & Media Relations section under the Events page.

"These data show that single doses of DNL593 result in substantial increases in CSF progranulin levels suggesting brain delivery of DNL593 was achieved and has the potential to address progranulin deficiency, which drives disease progression in people living with FTD-GRN," said Carole Ho, M.D., Chief Medical Officer at Denali. "Together with the safety profile to date, these results support initiation of dosing in participants with FTD-GRN and underscore the potential of our Protein Transport Vehicle (PTV) platform to deliver biotherapeutics across the blood-brain barrier. As the study progresses, we look forward to learning more about how DNL593 may impact patients with this devastating neurogenerative disease who have no approved treatment options."

As previously announced, this Phase 1/2 study is a multicenter, randomized, placebo-controlled study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of DNL593. The study is divided into three parts: In Part A, 35 participants in five cohorts received either single ascending doses of DNL593 or placebo; Part B will evaluate participants with FTD-GRN over 25 weeks; Part C is an optional 18-month open-label extension period available for all participants who complete part B. More information about the study (NCT05262023) is available here.

**About 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 TAK-594/DNL593 (PTV:PGRN)**
TAK-594/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*.[1] 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 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 receptor, which are expressed at the blood-brain barrier and are designed to 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 for neurodegenerative diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the blood-brain barrier 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 initiation of dosing in participants with FTD-GRN; 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; the potential benefits of, likelihood of success of, and expectations related to Denali's collaboration with Takeda; and statements made by Denali's Chief Medical 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: 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 Part B and Part C of 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 Forms 10-K and 10-Q filed with the Securities and Exchange Commission (SEC) on February 28, 2022 and August 8, 2022, 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.

**Reference:**
1. Logan T. et al. "Rescue of lysosomal storage disorder caused by Grn loss of function with a brain penetrant progranulin biologic" *Cell* 2021 Sep 2;184(18):4651-4688.

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