



Denali Therapeutics Announces Positive Clinical Results and Regulatory Progress for Development Programs in Amyotrophic Lateral Sclerosis (ALS)

October 6, 2021

- eIF2B activator DNL343 achieved safety and biomarker goals in a Phase 1 study in healthy volunteers; a Phase 1b study began in individuals with ALS in Q3 2021
- Fast Track designation granted by the U.S. Food and Drug Administration (FDA) to SAR443820/DNL788, a RIPK1 inhibitor, for the treatment of ALS; Sanofi to initiate Phase 2 study in individuals with ALS in Q1 2022
- Denali to host webinar for analysts and investors today, October 6, at 4:30 p.m. Eastern Time

SOUTH SAN FRANCISCO, Calif., Oct. 06, 2021 (GLOBE NEWSWIRE) -- [Denali Therapeutics Inc.](https://www.denali-therapeutics.com/) (NASDAQ: DNL), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for neurodegenerative diseases, today announced positive Phase 1 clinical results and regulatory progress for two investigational small molecule therapeutics in development for the treatment of amyotrophic lateral sclerosis (ALS) at the 2021 Annual Northeast ALS (NEALS) Meeting being held virtually, October 6-7.

"Effective treatment options are a critical unmet medical need for people living with ALS," said Carole Ho, M.D., Denali's Chief Medical Officer. "DNL343 and SAR443820 are designed to modulate distinct biological pathways implicated in ALS, including the integrated stress response and inflammation, respectively. We are pleased that the data generated preclinically and in Phase 1 studies support clinical investigation of both molecules as potential treatments for individuals with ALS."

"We're very encouraged by the initial results of the Phase 1 study of SAR443820 for the treatment of ALS," said Nazem Atassi, M.D., Sanofi's Global Head of Early Neurodevelopment. "ALS is a devastating disease for patients and their families, with no available cure or effective treatment for slowing its progression. We look forward to launching the Phase 2 HIMALAYA trial in adults with ALS in early 2022 and to achieving our ultimate goal of helping people living with ALS."

Highlights from eIF2B activator DNL343 clinical and preclinical data presented at NEALS

Denali presented positive results from a Phase 1 study in healthy volunteers (n=95) in which safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single and multiple ascending doses of DNL343 were evaluated. The results demonstrated that DNL343 was generally well tolerated for up to 14 days of dosing, with robust distribution in the central nervous system (CNS) and predictable dose-related increases in DNL343 exposure with a PK profile supporting once daily dosing. Biomarker assessments were also made as related to the cellular integrated stress response (ISR). The ISR is a biological pathway implicated in ALS and other diseases. After healthy volunteers were treated with DNL343, samples of their blood cells were subjected to stress *ex vivo*, and robust changes in biomarkers of the ISR were observed, confirming pathway engagement.

Denali also presented preclinical data in a mouse model of vanishing white matter (VWM) disease, a genetic and progressive disorder that causes severe neurological symptoms after exposure to certain stressors. eIF2B activity is reduced in the VWM disease model leading to chronic activation of the ISR, making this a relevant model for demonstrating target engagement and ISR modulation by DNL343. After treatment with DNL343, body weight and motor function were normalized in these mice. Furthermore, ISR gene expression and stress response protein levels were reduced in both peripheral tissues as well as the brain. A similar PK/PD relationship was observed in mice and in humans, supporting DNL343 dose selection in the ongoing Phase 1b study in participants with ALS.

The Phase 1b study ([NCT05006352](https://clinicaltrials.gov/ct2/show/study/NCT05006352)) is a multicenter, randomized, placebo-controlled, double-blind, 28-day study followed by an 18-month open-label extension, designed to evaluate the safety, PK and PD of DNL343 in approximately 30 participants with ALS. Dosing in this study began in the third quarter of 2021.

Highlights from RIPK1 inhibitor SAR443820 clinical trial design presentation at NEALS and Fast Track Designation

Denali's partner Sanofi presented plans for a Phase 2 study of RIPK1 inhibitor SAR443820 in participants with ALS based on positive results of a Phase 1 study in healthy volunteers. In that study, robust target engagement was demonstrated at doses that were generally well tolerated. The Phase 2 study, named **HIMALAYA**, is a multi-center, randomized, double-blind, placebo-controlled study, followed by an open-label long-term extension, to evaluate the efficacy and safety of SAR443820 in adult participants with ALS. This Phase 2 study is expected to commence in the first quarter of 2022.

The U.S. FDA has granted Fast Track designation to SAR443820 for the treatment of ALS. Fast Track is an FDA process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. Fast Track designation may allow for early and frequent communication with the FDA regarding the development of SAR443820 for the treatment of ALS. This designation also enables rolling review of the marketing application.

About the eIF2B activator DNL343

Modulation of eIF2B activity with DNL343 is a novel and targeted investigational approach with first-in-class potential for the

treatment of ALS. eIF2B is an intracellular protein complex that regulates protein synthesis and is required for neuronal health and function. When neurons experience stress, as occurs in ALS, eIF2B activity is suppressed. This leads to impaired protein synthesis and results in the formation of "stress granules," which are thought to be a precursor of TDP-43 aggregation, a hallmark pathology in ALS. DNL343 is designed to activate eIF2B and thereby restore protein synthesis, disperse TDP-43 aggregates, and improve neuronal survival. DNL343 is an investigational therapeutic and has not been approved by any regulatory authority for any commercial use.

About the RIPK1 Inhibitor SAR443820/DNL788

SAR443820/DNL788 is a novel, CNS-penetrant, small molecule inhibitor of RIPK1, a critical signaling mediator of necroptotic cell death, cytokine release, and inflammatory pathways. Denali and Sanofi entered into a broad collaboration in October 2018 for the global development and commercialization of RIPK1 inhibitors. This includes CNS-penetrant molecules such as SAR443820/DNL788, which was evaluated in a Phase 1 study in healthy volunteers, with potential development for neurological indications such as ALS, multiple sclerosis (MS) and Alzheimer's disease (AD). Sanofi leads Phase 1 and Phase 2 development of SAR443820/DNL788 for ALS and MS and leads co-development of SAR443820/DNL788 with Denali in Phase 3 clinical trials for ALS, AD and MS. SAR443820/DNL788 is an investigational therapeutic that has not been approved by any regulatory authority for any commercial use.

Denali Webinar for analysts and investors on October 6, 2021, at 4:30 p.m. ET

Denali plans to host a webinar for analysts and investors to highlight development programs in ALS and frontotemporal dementia (FTD) on October 6, 2021, starting at approximately 4:30 p.m. Eastern Time. During the webinar, Denali will review the NEALS presentations related to its investigational small molecule therapeutics DNL343, an eIF2B activator, and SAR443820, a RIPK1 inhibitor. Denali will also review preclinical data on DNL593 (PTV:PGRN), its Transport Vehicle (TV)-enabled biotherapeutic in development for FTD-GRN, which was recently [published](#) in *Cell*. The webinar will be available on Denali's corporate website on the Events page under the Investor section at <https://www.denalitherapeutics.com/investors/events>. An archived replay of the webinar will be available for at least 30 days following the event. Preregistration for the webinar can be accessed [here](#).

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 plans, timelines and expectations related to DNL343, SAR443820/DNL788; the DNL343 ongoing Phase 1b study and the planned Phase 2 study of SAR443820/DNL788; expectations regarding Denali's product candidates and the therapeutic potential of DNL343 and SAR443820/DNL788; statements made by Denali's Chief Medical Officer; and statements made by Sanofi's Global Head of Early Neurodevelopment. 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 directly or indirectly by the evolving COVID-19 pandemic; Denali's and its partners' ability to enroll patients in its ongoing and future clinical trials; the potential for clinical trial results of DNL343 or SAR443820/DNL788 to differ from preclinical, preliminary or expected results; the risk that the expected benefits of Fast Track designation for SAR443820/DNL788 will not materialize; the risk that DNL343 or SAR443820/DNL788 may cause serious adverse events; the risk that DNL343 and SAR443820/DNL788 may not in the future receive regulatory approval as a treatment for amyotrophic lateral sclerosis (ALS) or other indications for which they are being developed; 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 and its partners' ability to complete the development and, if approved, commercialization of its product candidates; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; Denali's and its partners' ability to conduct or complete clinical trials on expected timelines; 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; and other risks, including those described in Denali's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 4, 2021, Denali's Annual Report on Form 10-K filed with the SEC on February 26, 2021, and Denali's future reports to be filed with the SEC. The forward-looking statements in this press release are based on information available to Denali as of the date hereof. Denali disclaims any obligation to update any forward-looking statements, except as required by law.

Investor Relations

Contact:

Laura Hansen, Ph.D.
Vice President, Investor
Relations
(650) 452-2747

Media Contacts:

Lizzie Hyland
(646) 495-2706
lizzie.hyland@fgh.com
or

hansen@dnli.com

Morgan Warners
(202) 295-0124
morgan.warners@fgh.com



Source: Denali Therapeutics Inc.