# Denali Therapeutics Announces Achievement of RIPK1 Milestone for Phase 2 Clinical Trial Initiation in Multiple Sclerosis by Sanofi

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- Partner Sanofi has commenced dosing in a Phase 2 clinical trial of SAR443820 (DNL788) in individuals with multiple sclerosis
- Denali to receive a milestone payment of $25 million from Sanofi for Phase 2 clinical trial initiation
- Development of RIPK1 inhibitor program continues in a broad range of central nervous system and peripheral inflammatory conditions

SOUTH SAN FRANCISCO, Calif., Jan. 25, 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 for the treatment of neurodegenerative diseases and lysosomal storage diseases, today announced that its partner Sanofi has commenced dosing in a Phase 2 study of SAR443820 (DNL788) in individuals with multiple sclerosis. SAR443820 is a central nervous system (CNS)-penetrant investigational small molecule inhibitor of RIPK1.

“Multiple sclerosis is a chronic and disabling, inflammation-mediated neurodegenerative disease with limited treatment options that target disease progression[1],” said Nazem Atassi, M.D., Global Head of Early Neurology Development at Sanofi. “RIPK1 inhibition with SAR443820 is a novel therapeutic approach that may reduce inflammation and cell death associated with disease progression in multiple sclerosis. SAR443820 has demonstrated robust target engagement and CNS penetration at doses that were generally well tolerated in Phase 1 studies in healthy volunteers, and we are eager to learn more from this Phase 2 study of SAR443820 in multiple sclerosis as we strive to bring innovative therapies to people with unmet medical needs.”

“Following the initiation of the Phase 2 HIMALAYA study in ALS with SAR443820 last year by Sanofi, this Phase 2 study in multiple sclerosis marks another important milestone for our RIPK1 program,” said Carole Ho, M.D., Chief Medical Officer at Denali. “We look forward to collaborating with Sanofi as we aim to make a meaningful difference for individuals living with neurodegenerative diseases by delivering novel treatment options.”

**About SAR443820 and Sanofi RIPK1 Inhibitor Collaboration**

In 2018, Denali and Sanofi entered into a broad partnership for the global development and commercialization of CNS-penetrant and peripherally restricted RIPK1 inhibitors. RIPK1 is a critical signaling protein in a canonical inflammatory and cell death pathway. Increased RIPK1 activity in the brain drives neuroinflammation and cell necroptosis and contributes to neurodegeneration. RIPK1 inhibition has been shown to have beneficial effects in preclinical models of amyotrophic lateral sclerosis (ALS), multiple sclerosis, Alzheimer's disease, and other diseases.

SAR443820 is a CNS-penetrant RIPK1 inhibitor and was discovered by Denali scientists. Sanofi leads Phase 1 and Phase 2 development of SAR443820 for ALS and multiple sclerosis and leads co-development of SAR443820 with Denali in Phase 3 clinical trials for ALS, multiple sclerosis and Alzheimer’s disease. Sanofi completed a Phase 1 trial of SAR443820 in healthy volunteers in which robust target engagement was demonstrated at doses that were generally well tolerated. Based on these results, Sanofi initiated the HIMALAYA global Phase 2 study of SAR443820 in ALS in 2022, with an anticipated enrollment of approximately 260 participants.

Under the collaboration agreement, Denali will receive a milestone payment of $25 million from Sanofi for initiation of the Phase 2 study with SAR443820 in multiple sclerosis. Denali is entitled to receive additional development and regulatory milestone payments. Denali will share profits and losses equally with Sanofi for CNS-penetrant products sold in the United States and China, and Denali is entitled to receive royalties on net sales for CNS-penetrant products sold outside of the United States and China.

Sanofi is also conducting two Phase 2 clinical studies with another RIPK1 inhibitor, SAR443122 (eclitasertib; DNL758), in cutaneous lupus erythematosus and ulcerative colitis. SAR443122 (eclitasertib) is a peripherally restricted RIPK1 inhibitor and was discovered by Denali scientists. Sanofi is responsible for the development and commercialization of SAR443122 (eclitasertib) and covers all costs related to the program. Denali is entitled to receive development, regulatory and sales milestone payments and royalties on product sales.

SAR443820 and SAR443122 (eclitasertib) are investigational therapeutics that have not been approved by any regulatory authority for any commercial use.

**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 and lysosomal storage 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 both Denali's and Sanofi's plans, timelines, expectations, and milestones related to SAR443820 (DNL788) and SAR443122 (DNL758); statements made by Denali's Chief Medical Officer; statements made by Sanofi's Global Head of Early Neurology Development; Denali's priorities, regulatory approvals, timing and likelihood of success and expectations regarding its collaborations; Denali's expectations regarding milestone payments and royalties on product sales; expectations regarding Denali's product candidates and the therapeutic potential of SAR443820 (DNL788) and SAR443122 (DNL758); and the ongoing Phase 2 studies of SAR443820 (DNL788) in ALS and SAR443122 (DNL758) in cutaneous lupus erythematosus and ulcerative colitis. 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 ongoing COVID-19 pandemic; Denali's early stages of clinical drug development; Denali's dependence on successful development of its BBB platform technology and TV-enabled product candidates; Denali's and its partners' ability to enroll patients in its ongoing and future clinical trials; the potential for clinical trial results of Denali's product candidates to differ from preclinical, early clinical, preliminary or expected results; 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; the risk that the expected benefits of Fast Track designation for SAR443820 (DNL788) will not materialize; the risk that SAR443820 (DNL788) and SAR443122 (DNL758) may cause serious adverse events, toxicities or other side effects; the risk that SAR443820 (DNL788) and SAR443122 (DNL758) may not in the future receive regulatory approval as a treatment for ALS, MS, Alzheimer's disease, cutaneous lupus erythematosus, ulcerative colitis, or other indications necessary to be commercialized; 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 on expected timelines; 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 BBB platform technology; 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 and 10-Q filed with the Securities and Exchange Commission (SEC) on February 28, 2022 and November 3, 2022, respectively, 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 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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[1] Multiple sclerosis: Diagnosis & treatment. Mayo Clinic website. Available at: https://www.mayoclinic.org/diseases-conditions/multiple-sclerosis/diagnosis-treatment/drc-20350274. Accessed January 2023.

Source: Denali Therapeutics Inc.