Denali Therapeutics Provides Broad Update on Its RIPK1 Program Partnered With Sanofi

June 9, 2020

- *Denali and Sanofi pause DNL747[(a)] clinical activities based on the totality of DNL747 data and a superior profile of backup compound DNL788[(b)]*
- *Denali and Sanofi intend to accelerate DNL788 for development in neurological indications, with plans to initiate clinical testing by early 2021*
- *Safety endpoints were met in Phase 1b patient studies with DNL747 in ALS and Alzheimer's disease, however further dose escalation to achieve higher levels of target inhibition may be limited by preclinical chronic safety data*
- *Sanofi successfully completed the Phase 1 healthy volunteer study with peripherally-restricted RIPK1 inhibitor DNL758[(c)], and further clinical studies in multiple indications are being planned*

SOUTH SAN FRANCISCO, June 09, 2020 (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 the results from its Phase 1b studies with small molecule RIPK1 inhibitor DNL747 in Alzheimer's disease and ALS, and provided a broad RIPK1 program update including DNL788 and DNL758.

"Together with our partner Sanofi, we have decided to pause clinical studies with DNL747 and focus our efforts on accelerating development of DNL788, which we believe has superior drug properties and a more rapid path toward proof-of-concept clinical studies in patients in multiple neurological indications," said Ryan Watts, Ph.D., CEO. "We'd like to thank all patients who took part in these studies. Your participation is critical in the ultimate success of developing medicines for these terrible diseases."

RIPK1, receptor-interacting serine/threonine-protein kinase 1, is a critical signaling protein in the TNF receptor pathway, which regulates inflammation and cell death in tissues throughout the body.

Data from 31 patients in two 29-day Phase 1b studies in Alzheimer's disease and ALS, and additional data from six ALS patients in an open label extension study, showed that DNL747 was safe and well tolerated at the dose tested with no significant treatment related adverse events. Target engagement of approximately 80% median inhibition of pRIPK1 in blood at trough drug concentration was achieved.

In parallel to the clinical studies, chronic toxicity studies with DNL747 in cynomolgus monkeys showed dose- and duration-dependent adverse preclinical findings at exposures higher than those tested in the clinic. These findings, which are considered off-target and molecule-specific, impact the ability to increase the dose of DNL747 and achieve higher levels of target inhibition without time consuming additional clinical safety studies in patients to evaluate the long-term safety and tolerability.

"Due to emerging evidence that higher levels of target inhibition may be required for maximizing efficacy, and challenges to achieving higher doses imposed by molecule-specific toxicity findings with DNL747, we are pausing additional studies with this molecule," said Carole Ho, M.D., Chief Medical Officer. "However, I am encouraged by the emerging pathway biomarker data in Alzheimer's disease and ALS patients, and our experience and learnings with DNL747 should allow us to progress quickly with clinical studies for DNL788. Importantly, DNL788 appears to have a superior preclinical therapeutic window compared to DNL747, facilitating development in multiple indications, including Alzheimer's disease, ALS and multiple sclerosis."

Data from the completed Phase 1 study with peripherally-restricted RIPK1 inhibitor DNL758 in healthy volunteer subjects display an encouraging profile, as the molecule appears safe and tolerable at doses tested. Denali partner Sanofi is responsible for development of DNL758 and is currently planning further clinical studies in multiple indications based on successful Phase 1 data.

[(a)] SAR443060, [(b)] SAR443820, [(c)] SAR443122

About Denali

Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the BBB for neurodegenerative diseases. Denali Therapeutics 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 Therapeutics is based in South San Francisco. For additional information, please visit http://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, plans, timelines and expectations related to DNL747, DNL788 and DNL758 of both Denali and Sanofi; Denali's and Sanofi's intentions to accelerate DNL788 for development in neurological indications, with plans to initiate clinical testing by early 2021; expectations regarding

development of DNL788 in multiple indications; plans for further clinical studies of DNL758 in multiple indications; and statements made by Denali's CEO and 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: any and all risks to Denali's business and operations caused directly or indirectly by the evolving COVID-19 pandemic; Denali's early stages of clinical drug development; Denali's ability to complete the development and, if approved, commercialization of its product candidates; Denali's ability to enroll patients in its ongoing and future clinical trials; Denali's reliance on third parties for the manufacture and supply its product candidates for clinical trials; the risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's collaboration agreements, including the collaboration agreement with Sanofi; Denali's dependence on successful development of its BBB platform technology; Denali's ability to conduct or complete clinical trials on expected timelines; the risk that preclinical profiles of Denali's product candidates, such as DNL788, may not translate in clinical studies, and 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 BBB 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; general economic and market conditions; and other risks and uncertainties, including those described in Denali's most recent Annual Report on Form 10-K, most recent Quarterly Report on From 10-Q 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.

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