Denali Therapeutics Announces Decision to Advance DNL151 into Late Stage Clinical Studies in Parkinson's Patients

August 6, 2020

- *DNL151 selected to advance into two late stage studies in Parkinson's disease in patients with a kinase activating mutation in LRRK2 and in patients with sporadic disease*
- *Denali and collaboration partner Biogen are finalizing DNL151 clinical development plans and intend to commence patient enrollment in 2021*

SOUTH SAN FRANCISCO, Calif., Aug. 06, 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 treatment of neurodegenerative diseases, today announced that DNL151 has been selected to progress into late stage studies in Parkinson's disease patients with a kinase activating mutation in LRRK2 and in sporadic Parkinson's disease patients.

"Safety and biomarker data from studies of our two LRRK2 molecules in Parkinson's patients support moving DNL151 into late stage clinical studies with the aim of addressing the devastating clinical decline and pathology of disease in Parkinson's patients," said Carole Ho, M.D., Chief Medical Officer. "Our collaboration partner Biogen is a respected leader in neurodegenerative diseases and brings deep scientific and development expertise in Parkinson's disease which will allow us to accelerate our development plan and we believe increase the likelihood of ultimate success."

LRRK2 is a regulator of lysosomal function, which is impaired in Parkinson's disease and may be restored by LRRK2 inhibition. Inhibition of LRRK2 activity may slow the progression of Parkinson's disease in patients with and without known genetic risks based on restoration of lysosomal function. Mutations in the LRRK2 gene can cause Parkinson's disease and are a major driver of lysosomal dysfunction, which contributes to neurodegeneration.

DNL151 has completed dosing of 162 healthy volunteers in an ongoing Phase 1 clinical study and 25 Parkinson's patients in a Phase 1b clinical study. Denali is currently completing further dose escalation cohorts in an expanded Phase 1 and an additional cohort in the Phase 1b study to define the full therapeutic window of the molecule. Based on the clinical data to date that have been generated in Europe, DNL151 appears to have an acceptable safety and tolerability profile, and has met desired target engagement goals. An Investigational New Drug application for DNL151 was cleared by the U.S. Food and Drug Administration in July 2020 and enables expansion of our clinical studies for DNL151 globally. Based on the totality of preclinical and clinical data to date, both DNL201 and DNL151 (two chemically distinct LRRK2 inhibitors) have met Denali's requirements to proceed into further late stage clinical studies. However, Denali has selected DNL151 due to pharmacokinetic properties that provide additional dosing regimen flexibility.

Denali and Biogen are working to finalize the clinical development plans for the LRRK2 program and intend to commence two separate Parkinson's disease studies, one in patients with a kinase activating mutation in LRRK2 and the other in patients with sporadic disease. Patient enrollment is expected to commence in 2021.

About Denali's LRRK2 program

Denali has two CNS-penetrant small molecules that inhibit LRRK2 in clinical studies, DNL201 and DNL151.

DNL 201 has successfully completed a Phase 1 study in 122 healthy volunteer subjects and a Phase 1b study in 28 Parkinson's disease patients. DNL201 has been generally safe and well tolerated in doses tested and met all target engagement and biomarker goals. Based on this, DNL201 has met the bar for progression into further clinical studies.

DNL151 has successfully completed dosing of 162 healthy volunteers in an ongoing Phase 1 study in healthy volunteer subjects and completed dosing in 25 Parkinson's disease patients in a Phase 1b clinical study. DNL151 met safety, target engagement and biomarker goals in the Phase 1 healthy volunteer study. Denali is currently completing further dose escalation cohorts in an expanded Phase 1 and Phase 1b study to define the full therapeutic window. Target and pathway engagement of greater than 50 percent and a dose-dependent reduction of BMP in urine of up to 50 percent were observed at clinically relevant doses in healthy volunteers. The DNL151 Phase 1b study (NCT04056689) in Parkinson's disease patients is a 28-day, multicenter, randomized, placebo controlled, double-blind clinical trial in patients with mild-to-moderate Parkinson's disease being conducted in the U.S. and Europe. Its purpose is to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, including target and pathway engagement biomarkers as well as certain exploratory clinical endpoints, after multiple oral doses of DNL151. To date, 25 patients have been enrolled in the study, and the protocol has been amended to expand the study with up to 10 additional patients. Both the Phase 1 healthy volunteer and Phase 1b Parkinson's patient studies are anticipated to complete in 2020.

Further information on clinical studies with DNL151, DNL201 and Denali's efforts in Parkinson's disease can be found on clinicaltrials.gov and EngageParkinsons.com – Denali's Parkinson's disease patient engagement website for patients, caregivers and healthcare professionals.

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 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 DNL 201, DNL151 and other LRRK2 inhibitor molecules; expectations regarding the proposed collaboration with Biogen; the potential benefits and results of Denali's collaboration agreement with Biogen; expectations regarding the commencement of, and timing of patient enrollment in, clinical trials; expectations regarding the timing of completion of ongoing clinical trials; 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: any and all risks to Denali's business and operations caused directly or indirectly by the evolving COVID-19 pandemic; the risks that the proposed transaction with Biogen may not be completed in a timely manner or at all; the possibility that certain closing conditions to the proposed transaction with Biogen will not be satisfied, including the finalization of a definitive collaboration agreement; risks related to obtaining the requisite regulatory approvals, including those required under antitrust laws; the risk of the occurrence of any event, change or other circumstance that could give rise to the termination of the agreements with Biogen (including without limitation the failure to timely obtain requisite regulatory approvals); Denali's early stages of clinical drug development; Denali's and its partners' ability to complete the development and, if approved, commercialization of its product candidates; Denali's and its partners' ability to enroll patients in clinical trials; Denali's reliance on third parties for the manufacture and supply its product candidates for clinical trials; Denali's dependence on successful development of its BBB platform technology; Denali's and its partners' ability to conduct or complete clinical trials on expected timelines; the risk that preclinical profiles of Denali's product candidates, such as DNL151, may not translate in clinical trials and that such product candidates may not sufficiently modify Parkinson's disease; 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 Form 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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Source: Denali Therapeutics Inc.