Denali Therapeutics Announces Advancement and Expansion of Its LRRK2 Inhibitor Clinical Program for Parkinson's Disease

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DNL201 Achieves Target Engagement, FDA Lifts Partial Clinical Hold on DNL201, and DNL151 Moves into Clinical Testing

SOUTH SAN FRANCISCO, Calif., Dec. 20, 2017 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (NASDAQ:DNLI), a biopharmaceutical company developing a broad portfolio of therapeutic candidates for neurodegenerative diseases, today announced that its small molecule inhibitor of leucine-rich repeat kinase 2 (LRRK2), DNL201, achieved, on average, greater than 90% inhibition of LRRK2 kinase activity observed at peak and greater than 50% inhibition at trough drug levels at the highest multiple dose tested in a healthy volunteer Phase 1 study. Based on a full review of the clinical data from this ongoing study, and additional preclinical data, the FDA has removed the previously imposed partial clinical hold.

LRRK2 inhibition was measured by two independent blood-based biomarker assays of LRRK2 activity: phosphorylation of LRRK2 at Serine 935 and phosphorylation of the LRRK2 substrate Rab10. Both markers reflect the function of LRRK2 kinase activity and Rab phosphorylation is linked to lysosomal dysfunction associated with Parkinson's disease. In addition, robust central nervous system penetration of DNL201 has been achieved as demonstrated by measurement of DNL201 in the cerebrospinal fluid (CSF). These data, in combination with pharmacokinetics/pharmacodynamics (PK/PD) modeling, indicate robust and sustained target engagement of LRRK2 in brain.

Denali also announced that it has commenced dosing of its second small molecule inhibitor of LRRK2, DNL151, in healthy volunteers in the Netherlands. Denali now has two distinct small molecules targeting LRRK2 inhibition in human clinical testing for Parkinson's disease.

Denali plans to select either DNL201 or DNL151 to move into studies in Parkinson's disease patients carrying a LRRK2 mutation after completion of Phase 1 healthy volunteer studies for both molecules. In the ongoing studies in healthy volunteers, Denali is investigating safety and tolerability, PK and PD in blood and CSF, and characterizing a biomarker to estimate target engagement in brain.

"Mutations in LRRK2 are a major risk factor for Parkinson's disease. Targeting this degenogene represents a promising approach to develop disease modifying medicines for patients suffering from this terrible disease," said Ryan Watts, Ph.D., CEO. "By restoring LRRK2 activity to normal levels, we believe we can reverse lysosomal dysfunction, which could potentially benefit both patients with LRRK2 mutations, as well as idiopathic Parkinson's disease patients who exhibit lysosomal dysfunction," said Dr. Watts.

"Our robust biomarker assay allows us to establish and monitor LRRK2 target and pathway engagement, and assess the exposures required to reach desired target inhibition. We have demonstrated significant inhibition of LRRK2 kinase activity with DNL201, which gives us confidence to proceed with further clinical testing," said Carole Ho, M.D., Chief Medical Officer.

About Denali

Denali is a biopharmaceutical company developing a broad portfolio of therapeutic candidates for neurodegenerative diseases. 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 express or implied in this press release include, but are not limited to, plans to progress either DNL201 or DNL151 into studies in Parkinson's disease patients following completion of Phase 1 healthy volunteer studies for both molecules, results of targeting mutations of LRRK2 to develop disease modifying medicines for Parkinson's disease patients, the effects of restoring LRRK2 activity to normal levels and potential benefits to both patients with LRRK2 mutations and idiopathic Parkinson's disease who exhibit lysosomal dysfunction, and Denali's plans to conduct further clinical testing in this area. 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 its product candidates; Denali's dependence on successful development of its BBB platform technology and product candidates currently in its core program; Denali's ability to conduct or complete clinical trials on expected timelines; the uncertainty that any of Denali's 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; and other risks, including those described in Denali's Prospectus filed with the SEC on December 8, 2017. 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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