Denali Therapeutics Presents Positive Results from Phase 1 and Phase 1b Studies of Its LRRK2 Inhibitor, BIIB122/DNL151, Supporting Late-Stage Development Plans in Parkinson's Disease

May 1, 2021

- Treatment with BIIB122/DNL151 achieved robust reductions in biomarkers of target engagement and pathway engagement in healthy volunteers and patients with Parkinson's disease
- BIIB122/DNL151 demonstrated a safety profile supporting continued development in patients with Parkinson's disease
- Data support once daily oral dosing with BIIB122/DNL151
- Denali and Biogen plan to advance BIIB122/DNL151 into late-stage development in patients with Parkinson's disease by year-end 2021

SOUTH SAN FRANCISCO, Calif., May 01, 2021 (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 final results from Phase 1 and Phase 1b studies of its small molecule LRRK2 inhibitor, BIIB122/DNL151, which is being developed in collaboration with Biogen as a potential treatment of Parkinson's disease. Safety and biomarker goals were met in both studies, supporting plans to advance BIIB122/DNL151 into late-stage clinical development in Parkinson's disease by year-end 2021. The results will be presented at the International Association of Parkinsonism and Related Disorders Virtual Congress, being held May 1-4.

Results from the Phase 1 study of healthy volunteers (N=184) and the Phase 1b study of patients with Parkinson's disease (N=36) showed achievement of robust target and pathway engagement with BIIB122/DNL151 treatment as measured by pS935 LRRK2 and pT73 Rab10 (pRab10), respectively. In addition, a dose-dependent reduction in urine of the lysosomal lipid BMP, a biomarker of lysosomal function, was achieved with BIIB122/DNL151 treatment, providing peripheral evidence supporting improvement of lysosomal function. BIIB122/DNL151 was generally well tolerated across a broad range of doses for up to 28 days, the longest treatment duration in both studies.

"The Phase 1/1b results show that treatment with BIIB122/DNL151 achieved robust LRRK2 target engagement and downstream biological pathway engagement at doses that were generally well tolerated in healthy volunteers and patients with Parkinson's disease," said Carole Ho, M.D., Chief Medical Officer at Denali. "This rigorous Phase 1/1b dataset exemplifies Denali's approach of using biomarkers to guide drug development for neurodegenerative diseases and supports our plans with Biogen to advance BIIB122/DNL151 into late-stage clinical development for the potential treatment of Parkinson's disease."

Mutations in the LRRK2 gene can cause Parkinson's disease. LRRK2 is a regulator of lysosomal function, which is impaired in Parkinson's disease and may contribute to neurodegeneration. 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.

"LRRK2 is a novel and promising target for the development of new, potentially disease-modifying therapies that have not yet been available as treatment options for people living with Parkinson's disease," said Alfred W. Sandrock, Jr., M.D., Ph.D., Executive Vice President, Research & Development at Biogen. "Denali's Phase 1 and Phase 1b data support BIIB122/DNL151 as a potential first-in-class oral therapy that may slow the progression of Parkinson's disease. We look forward to continued collaboration with Denali as we finalize plans for late-stage development."

Summary of key biomarker results from Phase 1 and Phase 1b studies

A total of 184 healthy volunteers (145 BIIB122/DNL151, 39 placebo) were enrolled in the Phase 1 study and treated with single or once daily multiple doses ranging from 15 mg to 300 mg for up to 28 days or twice daily doses of up to 400 mg for 14 days. A total of 36 patients with Parkinson's disease (26 BIIB122/DNL151, 10 placebo) were enrolled in the Phase 1b study and treated with once daily multiple doses up to 300 mg for 28 days.

In the Phase 1 and Phase 1b studies, a dose dependent robust reduction in pS935 of greater than or equal to 50% in whole blood was observed at doses of BIIB122/DNL151 greater than 70 mg in healthy volunteers and across all dose levels studied in patients (80 mg, 130 mg, and 300 mg given once daily for 28 days). This level of pS935 reduction observed is consistent with the magnitude of reduction required for normalization of increased LRRK2 kinase activity observed in Parkinson's patients with kinase activating LRRK2 mutations. In addition, across both studies, a robust reduction in pS935 of greater than or equal to 80% was observed at doses of BIIB2122/DNL151 greater than or equal to 225 mg.

Further, a dose dependent reduction in phosphorylation of Rab10, a substrate of LRRK2, was observed across the healthy volunteer cohorts in Phase 1, and a reduction of greater than or equal to approximately 50% was observed at all dose levels studied in patients in Phase 1b. After normalizing for total LRRK2 levels, pRab10 was elevated by approximately 2-fold in patients with sporadic Parkinson's disease and in LRRK2 mutation carriers compared with healthy volunteers. Thus, the levels of pRab10 reduction observed in the Phase 1b study are consistent with the magnitude required for normalization of pRab10 levels in patients with Parkinson's disease.

Finally, in both healthy volunteers and patients with Parkinson's disease, treatment with BIIB122/DNL151 was associated with a dose-dependent reduction in urine lysosomal lipid 22:6-bis[monoacylglycerol] phosphate (BMP), a marker of peripheral lysosomal function, as measured from baseline to steady-state.

Summary of BIIB122/DNL151 safety and tolerability profile in Phase 1 and Phase 1b studies

BIIB122/DNL151 was generally well tolerated in healthy volunteers and patients with Parkinson's disease. No serious adverse events were observed. The majority of healthy volunteers and patients with treatment-emergent adverse events (TEAEs) experienced mild to moderate TEAEs. Two healthy volunteers in the Phase 1 study who received 250 mg twice daily and 400 mg twice daily, respectively, discontinued with symptoms including nausea and headache considered related to study drug. Two patients in the Phase 1b study discontinued on the first study day: one who received 130 mg once daily experienced severe asymptomatic hypotension, considered by the investigator as being unrelated to study drug (pre-existing hypotension), and another patient who received 300 mg once daily experienced mild hypotension and orthostatic hypotension with mild dizziness. In all discontinuations, symptoms resolved with discontinuation of therapy. There were no clinically meaningful changes in pulmonary or renal function in either study.

About LRRK2 and BIIB122/DNL151

Mutations in leucine-rich repeat kinase 2 (LRRK2), a regulator of lysosomal function, are one of the most common genetic risk factors in Parkinson's disease. Specific LRRK2 mutations increase kinase activity, resulting in phosphorylation of Rab GTPases (phosphorylated Rab [pRab]) and subsequent lysosomal dysfunction, and associated Parkinson's disease pathogenic changes. Both increased LRRK2 activity and pRab have also been observed in people with Parkinson's disease independent of LRRK2 mutation status. LRRK2 inhibition can restore lysosomal function and reduce toxicity in models of Parkinson's disease. BIIB122/DNL151 is a potent, selective, central nervous system–penetrant LRRK2 kinase inhibitor under investigation for treatment of Parkinson's disease. Denali and Biogen plan to advance BIIB122/DNL151 into two late-stage studies in Parkinson's disease: one in Parkinson's patients who carry LRRK2 mutations and the other in Parkinson's patients independent of mutation status. BIIB122/DNL151 has not been approved by any Health Authority.

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 Denali's progress and business plans; plans, timelines and expectations related to BIIB122/DNL151 of both Denali and Biogen, including with respect to initiation of late-stage clinical development; the potential of BIIB122/DNL151 to be a treatment for Parkinson's disease and a first-in-class oral therapy; the potential benefits and likelihood of success of, activity under, and expectations related to Denali's collaboration with Biogen; and statements made by Denali's Chief Medical Officer and Biogen's Executive Vice President, Research & Development. 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; risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's agreements with Biogen; Denali's early stages of clinical drug development; Denali's and Biogen's ability to advance and complete the development of BIIB122/DNL151; Denali's and Biogen's ability to initiate, enroll patients in, conduct and complete the planned clinical trials of BIIB122/DNL151 on expected timelines; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; Denali's dependence on successful development of its blood-brain barrier platform technology and its current programs and product candidates; the potential for the planned clinical trials of BIIB122/DNL151 to differ from preclinical, early clinical, preliminary or expected results; the risk of significant adverse events, toxicities or other undesirable side effects; the uncertainty that product candidates will receive regulatory approval necessary to be commercialized; 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 Annual Report on Form 10-K filed with the Securities and Exchange Commission (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
hansen@dnli.com

Media Contacts:

Lizzie Hyland
(646) 495-2706
lhyland@gpg.com

or

Morgan Warners
(202) 295-0124
mwarners@gpg.com

Source: Denali Therapeutics Inc.