Biogen and Denali Therapeutics Announce Initiation of the Phase 3 LIGHTHOUSE Study in Parkinson's Disease Associated with LRRK2 Pathogenic Mutations

October 3, 2022

- Global Phase 3 study to evaluate efficacy and safety of BIIB122, a small molecule inhibitor of LRRK2
- LRRK2 mutations are one of the most common genetic drivers of Parkinson's disease
- Targeting LRRK2 has the potential to impact the underlying biology and slow the progression of Parkinson's disease

CAMBRIDGE, Mass. and SOUTH SAN FRANCISCO, Calif., Oct. 03, 2022 (GLOBE NEWSWIRE) -- Biogen Inc. (Nasdaq: BIIB) and Denali Therapeutics Inc. (Nasdaq: DNLI) today announced that dosing has commenced in the global Phase 3 LIGHTHOUSE study to evaluate the efficacy and safety profile of BIIB122 (DNL151), as compared to placebo in approximately 400 participants with Parkinson's disease and a confirmed pathogenic mutation in the leucine-rich repeat kinase 2 (LRRK2) gene.

The primary endpoint of the LIGHTHOUSE study is time to confirmed worsening, as assessed using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) over the treatment period, up to 180 weeks. Participants will be randomized to receive oral BIIB122 or placebo once daily.

"Mutations in the LRRK2 gene comprise the most frequent mutations found in Parkinson's disease, indicating that LRRK2 inhibition may be a promising therapeutic approach to the disease," said Samantha Budd Haeberlein, Ph.D., Head of Neurodegeneration Development at Biogen. "The LIGHTHOUSE study will specifically recruit individuals with a pathogenic mutation in LRRK2, enabling us to test the genetic hypothesis and implicated lysosomal pathway. The LIGHTHOUSE study is the largest study ever undertaken in individuals with Parkinson's disease caused by a LRKK2 mutation."

BIIB122 is an investigational small molecule inhibitor of LRRK2 that was discovered and initially developed by Denali. Denali and Biogen are co-developing and co-commercializing BIIB122 for the potential treatment of Parkinson's disease.

"In collaboration with Biogen, we are excited to be pursuing the potential of LRRK2 inhibition as an effective treatment for Parkinson's disease," said Carole Ho, M.D., Chief Medical Officer of Denali. "The initiation of the Phase 3 LIGHTHOUSE study marks an important milestone in the BIIB122 development program. Together with the recent initiation of the Phase 2b LUMA study in early-stage Parkinson's disease, we hope to have the opportunity to bring a novel therapeutic option to people living with Parkinson's disease."

More information about LIGHTHOUSE (NCT05418673) is available at ClinicalTrials.gov.

About LRRK2 and BIIB122
Following discovery of the LRRK2 mutation as a pathogenic genetic factor for Parkinson's disease, further research has uncovered that it has the potential to be a novel therapeutic target for Parkinson's disease. Mutations in leucine-rich repeat kinase 2 (LRRK2) account for 4-5% of familial and 1-2% of sporadic Parkinson's disease. [1,2]

BIIB122 is a selective, central nervous system-penetrant small molecule inhibitor of LRRK2 that is hypothesized to improve lysosomal dysfunction. BIIB122 is an investigational drug that is not approved by any regulatory authority, and its safety and efficacy have not been established.

About Biogen
As pioneers in neuroscience, Biogen discovers, develops, and delivers worldwide innovative therapies for people living with serious neurological diseases as well as related therapeutic adjacencies. One of the world's first global biotechnology companies, Biogen was founded in 1978 by Charles Weissmann, Heinz Schaller, Sir Kenneth Murray, and Nobel Prize winners Walter Gilbert and Phillip Sharp. Today, Biogen has a leading portfolio of medicines to treat multiple sclerosis, has introduced the first approved treatment for spinal muscular atrophy, and developed the first and only approved treatment to address a defining pathology of Alzheimer's disease. Biogen is also commercializing biosimilars and focusing on advancing one of the industry's most diversified pipelines in neuroscience that will transform the standard of care for patients in several areas of high unmet need.

In 2020, Biogen launched a bold 20-year, $250 million initiative to address the deeply interrelated issues of climate, health, and equity. Healthy Climate, Healthy Lives™ aims to eliminate fossil fuels across the company's operations, build collaborations with renowned institutions to advance the science to improve human health outcomes, and support underserved communities.

We routinely post information that may be important to investors on our website at www.biogen.com. Follow us on social media - Twitter, LinkedIn, Facebook, YouTube.

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.

Biogen Safe Harbor
This press release contains forward-looking statements, made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, including statements relating to the potential benefits and results that may be achieved through Biogen's collaboration with Denali; the potential benefits, safety and efficacy of BIIB122 (DNL151) and other LRRK2 inhibitor molecules; the clinical development program for BIIB122 (DNL151) and other LRRK2 inhibitor molecules; the potential benefits of Denali's TV technology platform and TV programs including its ATV: anti-amyloid beta program; the treatment of Parkinson's disease; the potential of Biogen's commercial business and pipeline programs; Biogen's strategy and plans; the potential treatment of neurological and neurodegenerative diseases; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "goal," "intend," "may," "plan," "potential," "possible," "will," "would" and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. Results in early stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including, without limitation: risks that the proposed transaction will be completed in a timely manner or at all; the possibility that certain closing conditions to the proposed transaction will not be satisfied; uncertainty as to whether the anticipated benefits of the proposed collaboration can be achieved; risks of unexpected hurdles, costs or delays; uncertainty of success in the development and potential commercialization of BIIB122 (DNL151) and other undisclosed neurological targets, which may be impacted by, among other things, unexpected concerns that may arise from additional data or analysis, the occurrence of adverse safety events, failure to obtain regulatory approvals in certain jurisdictions, failure to protect and enforce Biogen's data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; third party collaboration risks; and the direct and indirect impacts of the ongoing COVID-19 pandemic on Biogen's business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement, as well as the risks factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements are based on Biogen's current beliefs and expectations and speak only as of the date of this press release. Biogen does not undertake any obligation to publicly update any forward-looking statements, whether as a result of new information, future developments or otherwise.

Denali Safe Harbor
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), including with respect to the ongoing Phase 2b LUMA study and the Phase 3 LIGHTHOUSE study; the potential of BIIB122 (DNL151) to be a treatment for Parkinson's disease; the potential for LRRK2 inhibition to impact the underlying biology or slow the progression of Parkinson's disease in certain patients; 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 Head of Neurodegeneration 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 transition to a late stage clinical drug development company; Denali's and Biogen's ability to advance and complete the development and, if approved, commercialization of BIIB122 (DNL151); Denali's and Biogen's ability to initiate, enroll patients in, conduct, and complete the ongoing and planned clinical trials, including the Phase 2b LUMA and Phase 3 LIGHTHOUSE studies 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 risk that preclinical profiles of Denali's product candidates may not translate in clinical trials; the potential for the ongoing and 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 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 most recent Annual and Quarterly Reports filed on Forms 10-K and 10-Q filed with the Securities and Exchange Commission (SEC) on February 28, 2022 and August 8, 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 does not undertake 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.

References:

1. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol*. 2008;7(7):583-90.

2. Hernandez DG, Reed X, Singleton AB. Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. *J Neurochem*. 2016;139 Suppl 1:59-74. Epub 2016/04/18.

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Source: Denali Therapeutics Inc.