# Denali Therapeutics Receives Orphan Drug and Rare Pediatric Disease Designation for DNL310, and Expands its Portfolio of Brain Penetrant Enzyme Replacement Programs

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- *DNL310 on track to enter Phase 1/2 clinical study in Hunter Syndrome patients in 2020*
- *DNL310 utilizes Denali's proprietary blood-brain barrier crossing enzyme transport vehicle ("ETV") technology*
- *Two additional ETV-enabled enzyme replacement programs were advanced to pre-clinical testing*

SOUTH SAN FRANCISCO, Calif., June 11, 2019 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (NASDAQ: DNLI), a biopharmaceutical company developing a broad portfolio of product candidates for neurodegenerative diseases, today announced that the FDA granted Orphan Drug Designation ("ODD") and Rare Pediatric Disease Designation for Denali's DNL310 program, which Denali is developing for patients with mucopolysaccharidosis II ("MPS II" or Hunter Syndrome).

DNL310, or ETV:IDS, is a recombinant form of the iduronate 2-sulfatase ("IDS") enzyme engineered to cross the blood-brain barrier ("BBB") using Denali's proprietary ETV technology. DNL310 is intravenously ("i.v.") administered and intended to improve overall clinical manifestations of Hunter Syndrome, including neurological symptoms, which are not adequately addressed by currently approved therapies.

Hunter Syndrome is a lysosomal storage disease ("LSD") caused by a genetic deficiency of the IDS enzyme. Approximately two-thirds of patients with Hunter Syndrome suffer from progressive cognitive impairment in addition to other severe clinical manifestations. Standard enzyme replacement therapy ("ERT") does not result in sufficient brain concentrations to adequately address cognitive impairment. Pre-clinical studies with DNL310 in a relevant disease model demonstrated increased brain uptake and a more robust reduction of downstream markers of disease in the central nervous system compared to standard ERT.

The TV technology enables improved uptake and distribution of therapeutic antibodies, enzymes and other proteins in the brain after i.v. administration by binding to natural transport receptors in the vasculature of the brain. Pre-clinical studies with the TV technology have shown up to 30-fold increased uptake and superior pharmacological activity compared to standard antibodies, enzymes and other proteins. Denali is developing a broad portfolio of biologic drug candidates that are enabled by its TV technology. Based on pre-clinical proof of concept with DNL310, Denali initiated two additional ERT programs that are enabled by the TV technology.

"Hunter Syndrome is a debilitating condition, and current enzyme replacement therapies do not address the huge unmet medical need for treatment of the neurological manifestations of the disease," said Carole Ho, M.D., Chief Medical Officer. "Receiving ODD and Rare Pediatric Disease Designation from the FDA demonstrates our progress and commitment to developing a new treatment option for patients with this disease."

"The BBB has been a major challenge for the development of therapeutics for neurodegenerative diseases in the past. We believe that our BBB TV technology provides a non-invasive solution to deliver higher concentrations and broader distribution of protein-based therapeutics in the brain and will therefore improve the chance of success to achieve efficacy for patients with neurodegenerative diseases, including many lysosomal storage diseases," said Ryan Watts, Ph.D., CEO. "DNL310 is our most advanced program utilizing our TV platform and, once in clinical testing, could provide human proof of concept for this approach."

FDA grants Orphan Drug Designations to investigational therapies intended to treat, diagnose or prevent rare diseases and conditions affecting fewer than 200,000 people in the United States. Orphan drug designation provides benefits to drug developers including tax credits for clinical costs, exemptions from certain FDA fees, and seven years of marketing exclusivity if a marketing application is approved.

Rare Pediatric Disease Designation is granted by the FDA in the case of serious or life-threatening diseases affecting fewer than 200,000 people in the United States and primarily in individuals 18 years of age and younger. The sponsor of a drug with rare pediatric disease designation may be eligible for a priority review voucher upon approval of the drug that can be used to obtain priority review of a subsequent marketing application.

A Phase 1/2 patient study of DNL310 in Hunter Syndrome is planned for 2020.

**About Denali**

Denali is a biopharmaceutical company developing a broad portfolio of therapeutic candidates for neurodegenerative diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the blood-brain barrier and guiding development with biomarker monitoring to demonstrate target engagement and select patients. 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, plans to progress DNL310 into a Phase 1/2 clinical study in Hunter Syndrome patients in 2020, Denali's plans to conduct further clinical testing in this area, Denali's beliefs and expectations regarding the results of clinical testing and the benefits of its BBB TV technology, and statements made by Denali's CMO and CEO.

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; 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; and other risks, including those described in Denali's Annual Report on Form 10-K filed with the SEC on March 12, 2019, Denali's Quarterly Report on Form 10-Q filed with the SEC on May 8, 2019 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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