Denali Therapeutics Announces Publication of Two New Papers Describing Its Blood-Brain Barrier Delivery Technology in Science Translational Medicine

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- *Denali's "Transport Vehicle" technology enables broad distribution and improved exposure levels of therapeutic proteins throughout the brain*
- *Clinical proof of concept data with DNL310 (ETV:IDS), the first product candidate enabled by the transport vehicle technology, are expected in Hunter syndrome patients by late 2020*
- *Denali's EngageHunter.com website provides patients, caregivers and others information on Denali's investigational studies as well as developments in Hunter syndrome and Denali's approach to treating the disease*

SOUTH SAN FRANCISCO, Calif., May 27, 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 neurodegenerative diseases, today announced publication of two papers in *Science Translational Medicine ("STM")* . The papers describe the company's Transport Vehicle ("TV") technology, illustrate its ability to successfully deliver therapeutic proteins to the brain at levels sufficient for robust effects, and demonstrate the normalization of biomarkers in a disease model of Hunter syndrome. The company also provided an update on product candidate DNL310, its most advanced TV platform-enabled molecule.

"Engineering our medicines for brain delivery is one of our three scientific principles and is a core part of our strategy to defeat degeneration," said Ryan Watts, Ph.D., CEO. "We are excited to have two papers published in *STM* today. Taken together, these papers demonstrate the potential of our protein engineering approach, describe *in vivo* proof-of-concept studies for the TV platform in mice and non-human primates, and illustrate the application of the TV technology to enzymes for the treatment of lysosomal storage diseases. The peer-review and publication of these papers are important independent examinations of our platform and approach."

The BBB is essential in maintaining the brain's microenvironment and protecting it from harmful substances and pathogens circulating in the bloodstream. Historically, the BBB has posed significant challenges to drug development for central nervous system ("CNS") diseases by preventing most drugs from reaching the brain in therapeutically relevant concentrations.

Denali's TV platform is a proprietary technology designed to effectively deliver large therapeutic molecules such as antibodies, enzymes, proteins, and oligonucleotides across the BBB after intravenous administration. The TV technology is based on engineered Fc fragments that bind to specific transport receptors expressed at the BBB and are delivered to the brain. In animal models, antibodies and enzymes engineered with the TV technology have demonstrated more than 20-fold greater brain exposure than similar antibodies and enzymes without this technology. Improved exposure and broad distribution in the brain may enable higher, therapeutically relevant concentrations of product candidates, and thus increase therapeutic efficacy. The TV technology was designed and engineered by Denali, leveraging the partnership with F-star.

The first Denali-authored paper published in *STM* today, by Kariolis et al. entitled *"Brain delivery of therapeutic proteins using a novel Fc fragment blood-brain barrier transport vehicle in mice and monkeys,"* describes the development and engineering of the TV platform, and demonstrates how it increases brain exposure and distribution of certain antibodies in preclinical models including non-human primates.

The second paper by Ullman et al. entitled *"Brain delivery and activity of a lysosomal enzyme using a blood-brain barrier transport vehicle in mice,"* describes the applicability of the TV platform in delivering the lysosomal enzyme iduronate 2-sulfatase ("IDS") across the BBB, with more than 20-fold improved brain exposure and distribution throughout the brain. The administration of IDS using the TV technology in *in vivo* models leads to complete correction of downstream disease-relevant pathologies, including accumulation of lysosomal lipids, perturbed gene expression, neuroinflammation, and neuroaxonal damage.

These two Denali-authored *STM* publications and previous scientific publications by Denali are available on Denali Therapeutics' website here.

The data in these papers highlight the therapeutic potential of the TV platform and provide preclinical proof of concept for TV-enabled therapeutics to treat CNS diseases across a wide range of neurodegenerative diseases, lysosomal storage diseases, and other diseases in the brain, such as brain cancers.

DNL310 (ETV:IDS) is a recombinant form of the IDS enzyme engineered to cross the BBB using the Enzyme Transport Vehicle ("ETV") technology. The company expects to commence dosing in the first Hunter syndrome patient with DNL310 in a Phase 1/2 study shortly, and an interim data readout is expected by late 2020. This study is expected to provide proof of concept for the TV platform in humans. Further details on the DNL310 Phase 1/2 study are available here on ClinicalTrials.gov and at EngageHunter.com.

Additional preclinical programs in Denali's pipeline are enabled by the TV platform, with the most advanced programs being

PTV:PRGN and ATV:TREM2 for frontotemporal dementia and Alzheimer's disease, respectively, and ETV:SGSH for Sanfilippo syndrome.

About the EngageHunter.com Website

EngageHunter.com —theDenali Hunter syndrome patient engagement website—provides patients, caregivers, and advocates an online destination for emerging information about Hunter syndrome. In addition, the Engage Hunter website describes Denali's biomarker-driven approach in discovering and developing investigational therapies for Hunter syndrome patients.

The Engage Hunter website provides an avenue for registrants to engage with Denali's team to learn more about Denali sponsored clinical trials, including clinical studies with DNL310 in Hunter syndrome patients. Registrants will also receive communications from Denali on progress in emerging Hunter syndrome research and development insights, including information regarding future Denali investigational studies.

About Denali

Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier 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 https://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, the therapeutic potential of the TV platform; plans, timelines and expectations related to Denali's pipeline including DNL310, Denali's TV platform and any program enabled by Denali's TV platform; and statements made by Denali's Chief Executive 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; 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 ability to enroll patients in its ongoing and future clinical trials; Denali's reliance on third parties for the manufacture and supply its product candidates for clinical trials; the risk of the occurrence of any event, change or other circumstance that could give rise to the termination of Denali's collaboration agreements; Denali's dependence on successful development of its TV platform technology including the significance of the DNL310 Ph1/2 data to inform the therapeutic potential of the TV platform; Denali's ability to conduct or complete clinical trials on expected timelines; 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 blood-brain barrier 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 From 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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