Voyager Therapeutics Announces Preclinical Data for Huntington's Disease and Amyotrophic Lateral Sclerosis Programs at the Congress of the European Society of Gene and Cell Therapy

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One-time delivery of VY-HTT01 for Huntington's disease achieves significant reduction of HTT gene expression in deeper tissues and outer layers of the brain of large animals

One-time delivery of VY-SOD102 achieves significant reduction of SOD1 gene expression throughout a large animal spinal cord, including almost complete reduction in cervical motor neurons

CAMBRIDGE, Mass., Oct. 16, 2018 (GLOBE NEWSWIRE) -- Voyager Therapeutics, Inc. (NASDAQ: VYGR), a clinical-stage gene therapy company focused on developing life-changing treatments for severe neurological diseases, today announced data presentations at the Congress of the European Society of Gene and Cell Therapy (ESGCT) taking place October 16-19, 2018, in Lausanne, Switzerland.

For VY-HTT01, a novel delivery paradigm that targets both the putamen and thalamus significantly reduced *huntingtin*, or HTT, gene expression in both deeper tissues (caudate, putamen, and thalamus) and outer layers (cortex) of the brain of adult, non-human primates. Targeting both the putamen and thalamus leverages more extensive and preserved neuronal pathways to the cortex than delivery to the putamen alone, offering the potential of a one-time treatment with VY-HTT01 to address motor, cognitive and behavioral disabilities associated with Huntington's disease. Robust analyses including quantitative measurement in multiple tissue punches and in neurons captured by laser microdissection revealed that VY-HTT01 reduced HTT messenger RNA (mRNA) on average by 68% in the caudate, 67% in the putamen, 73% in the thalamus, and 32% in cortical neurons.

For VY-SOD102, a novel delivery paradigm comprising a one-time, intraparenchymal infusion to the cervical region of the spinal cord significantly reduced SOD1 throughout the spinal cord of the mini-pig, which has a spinal cord similar in length and diameter to the human spinal cord. This novel delivery approach with VY-SOD102 reduced SOD1 mRNA in the spinal cord on average by 70% and 50% in the cervical and thoracic regions, respectively, both regions critical for respiratory function, and 82% near the site of cervical injection. In addition, VY-SOD102 reduced SOD1 mRNA by 22% in the lumbar region.

"We are very excited by the robust reductions of disease-causing gene expression that were achieved as part of our latest delivery optimization efforts in both our Huntington's disease and ALS programs," said Dinah Sah, Ph.D., Voyager's chief scientific officer. "For Huntington's disease, targeting the putamen and thalamus generated significant knockdown of the target HTT in the deep tissues of the brain as well as in the cortex, offering the potential to address the most prominent manifestations of the disease. For our SOD1 ALS program, a direct infusion into the cervical region of the spinal cord generated significant knockdown of the target gene throughout the spinal cord, especially in the regions critical for respiratory function, including almost complete reduction of SOD1 near the site of injection. These data in large animals support our progress towards initiating human studies for both programs during 2019."

VY-HTT01 for Huntington's disease

Huntington's disease is a fatal, inherited neurodegenerative disease that results in the progressive decline of motor, cognitive and behavioral functions. The disease is caused by an inherited mutation in the HTT gene that leads to an expanded cytosine-adenine-guanine (CAG) repeat resulting in abnormal intracellular huntingtin protein aggregates and neuronal cell death in the cortex and striatum (putamen and caudate) of the brain. In Huntington's disease, early and prominent atrophy of the striatum can lead to loss of neuronal connections between the striatum and cortex. In contrast, the thalamus, as well as its widespread neuronal connections to the cortex, remain largely intact.

Voyager's gene therapy candidate, VY-HTT01, is composed of an adeno-associated virus capsid (AAV1) and proprietary transgene that harnesses the RNA interference pathway to selectively knock down, or reduce, levels of HTT mRNA. Direct delivery of VY-HTT01 to the brain with a one-time administration could potentially slow or halt the progression of this uniformly fatal disease. Preclinical studies in mouse models of Huntington's disease have demonstrated the safety and efficacy of AAV gene therapy targeting the knockdown of HTT mRNA.

VY-HTT01 data at ESGCT demonstrate significant reduction of HTT in the striatum and cortex

Title: "Robust Huntingtin knockdown in cortex and putamen in large mammals using a novel dosing paradigm with VY-HTT01, an AAV gene therapy targeting Huntingtin for the treatment of Huntington's disease" Poster 190

> At this year's ESGCT, Voyager presented results demonstrating significant reduction of HTT mRNA at five weeks post-dosing in adult non-human primates using an MRI-guided surgical delivery of VY-HTT01 and a novel delivery paradigm targeting both the putamen and thalamus. In addition to the putamen, targeting the thalamus leverages more extensive and more preserved neuronal pathways to the cortex than delivery to the putamen alone. The combined infusions into the putamen and thalamus have the potential to address the cognitive and motor functions associated with Huntington's disease. In adult non-human primates, this novel dosing paradigm with VY-HTT01 resulted in safe and significant suppression of HTT in the striatum and in cortical neurons, which are critical in the progression of disease.

Voyager performed robust analyses to assess HTT mRNA suppression in the striatum and cortex, including quantitative measurement in multiple tissue punches (30 per animal) and in cortical neurons captured by laser microdissection (16 samples of 900 neurons each, per animal). A combined infusion of VY-HTT01 into the putamen and thalamus significantly reduced HTT mRNA by 68% in the caudate, 67% in the putamen, and 73% in the thalamus, on average, as measured from tissue punches, and by 32% on average, in laser captured cortical neurons, which was also supported by in situ hybridization for HTT mRNA.

VY-HTT01 was well-tolerated in non-human primates at five weeks after dosing with no gene therapy-related changes in clinical pathology or adverse histopathological findings at the sites of administration associated with clinical signs. Further preclinical studies are underway with VY-HTT01 to support filing of an investigational new drug (IND) application in 2019.

VY-SOD102 for SOD1 ALS

ALS is a rapidly progressive, fatal disease characterized by the degeneration of motor neurons in the spinal cord and brain. Individuals with ALS typically develop progressive muscle weakness and atrophy, and early mortality most commonly results from respiratory failure.

Most ALS cases occur sporadically and with unknown cause, but in approximately 10 percent of patients, the cause is familial and can be linked to an identifiable genetic defect. An estimated 20 percent of familial cases can be attributed to mutations in the superoxide dismutase 1 gene (SOD1), leading to a toxic gain of function that is associated with a loss of motor neurons in the spinal cord.

VY-SOD102 is composed of an adeno-associated virus capsid (AAVrh10) and proprietary transgene that harnesses the RNA interference pathway to selectively knock down, or reduce, levels of SOD1 mRNA. VY-SOD102 has the potential to durably reduce the levels of toxic mutant SOD1 protein in the spinal cord to slow the progression of disease. Studies using transgenic mice expressing SOD1 mutations have demonstrated reduced neuropathology, improved motor behavior, and extension of survival with lowering of SOD1.

VY-SOD102 data at ESGCT demonstrate significant reduction of SOD1 in the spinal cord of large mammals

Title: “Robust SOD1 knockdown in large mammal spinal cord using a novel delivery paradigm with AAV gene therapy targeting SOD1 for the treatment of SOD1-ALS” Poster P185

At this year’s ESGCT, Voyager presented data on VY-SOD102 administered with a novel delivery paradigm comprising a one-time, intraparenchymal infusion after laminectomy to the cervical spinal cord of the Gottingen mini-pig, which has a spinal cord similar in length and diameter to the human spinal cord.

Voyager performed robust analyses to measure SOD1 mRNA suppression in the spinal cord, including quantitative measurement in multiple ventral horn tissue punches (32 per animal from 15 different spinal cord segments between cervical and lumbar regions). This delivery approach yielded safe and significant reduction of SOD1 at the site of infusion and throughout the spinal cord, most notably in the cervical and thoracic regions critical for respiratory function. This included reductions of SOD1 mRNA on average by 70% and 50% in the cervical and thoracic regions, respectively. Near the site of cervical injection, VY-SOD102 suppressed SOD1 mRNA on average by 82%, representing almost complete suppression of SOD1 mRNA. The robust reduction of SOD1 mRNA was supported by in-situ hybridization, which demonstrated almost complete suppression of SOD1 mRNA in cervical motor neurons. In addition, VY-SOD102 reduced SOD1 mRNA by 22% in the lumbar region. Further preclinical studies are underway with VY-SOD102 to support filing of an IND application in 2019.

Data presentations at this year’s ESGCT meeting can be found on the Events and Presentations page of the Investors and Media section of Voyager’s corporate website at www.voyagertherapeutics.com

About Voyager Therapeutics

Voyager Therapeutics is a clinical-stage gene therapy company focused on developing life-changing treatments for severe neurological diseases. Voyager is committed to advancing the field of AAV gene therapy through innovation and investment in vector engineering and optimization, manufacturing and dosing and delivery techniques. Voyager’s pipeline focuses on severe neurological diseases in need of effective new therapies, including Parkinson’s disease, a monogenic form of ALS called SOD1, Huntington’s disease, Friedreich’s ataxia, neurodegenerative diseases related to defective or excess aggregation of tau protein in the brain including Alzheimer’s disease and severe, chronic pain. Voyager has broad strategic collaborations with Sanofi Genzyme, the specialty care global business unit of Sanofi, AbbVie, and the University of Massachusetts Medical School. Founded by scientific and clinical leaders in the fields of AAV gene therapy, expressed RNA interference and neuroscience, Voyager Therapeutics is headquartered in Cambridge, Massachusetts.

Forward-Looking Statements

This press release contains forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995 and other federal securities laws. The use of words such as “may,” “might,” “will,” “would,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “undoubtedly,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward-looking statements. For example, all statements Voyager makes regarding the initiation, timing, progress and reporting of results of its preclinical programs and clinical trials and its research and development programs, its ability to advance its AAV-based gene therapies into, and successfully initiate, enroll and complete, clinical trials, the potential clinical utility of its product candidates, its ability to continue to develop its gene therapy platform, its ability to develop manufacturing capability for its products and successfully transition its manufacturing process, its ability to perform under existing collaborations with, among others, Sanofi Genzyme and AbbVie and to add new programs to its pipeline, its ability to enter into new partnerships or

collaborations, the sufficiency of its cash resources and the timing or likelihood of its regulatory filings and approvals, are forward looking. All forward-looking statements are based on estimates and assumptions by Voyager's management that, although Voyager believes to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that Voyager expected. Such risks and uncertainties include, among others, the initiation and conduct of preclinical studies and clinical trials; the availability of data from clinical trials; the expectations for regulatory submissions and approvals; the continued development of the gene therapy platform; Voyager's scientific approach and general development progress; and the availability or commercial potential of Voyager's product candidates. These statements are also subject to a number of material risks and uncertainties that are described in Voyager's most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission, as updated by its subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. Voyager undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

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