Voyager Therapeutics Announces Updates from Phase 1b Trial of VY-AADC01 for Advanced Parkinson's Disease

January 20, 2017

Cohort 3 Enrollment Complete with Increased Coverage of the Putamen Observed

Cohort 3 On Track for Six-Month Data Update Mid-2017

CAMBRIDGE, Mass., Jan. 20, 2017 (GLOBE NEWSWIRE) -- Voyager Therapeutics, Inc. (NASDAQ:VYGR), a clinical-stage gene therapy company developing life-changing treatments for severe diseases of the central nervous system (CNS), today announced updates regarding the Phase 1b trial of VY-AADC01 for patients with advanced Parkinson's disease.

"The clinical trial of VY-AADC01 is progressing well with all five patients in Cohort 3 successfully completing treatment," said Bernard Ravina, M.D., M.S., vice president of clinical development at Voyager Therapeutics. "The neurosurgeons are clearly gaining experience administering VY-AADC01 as evident by the increase in surgical coverage of the putamen achieved in Cohort 3 of 42% compared to 34% in Cohort 2 with similar infusion volumes. Cohort 1 achieved 21% coverage with a lower infusion volume. We are very encouraged by the increased surgical coverage of the putamen with VY-AADCO1 due to its high correlation with increased AADC enzyme activity. The consistency of coverage between patients and the overall favorable safety profile observed in this trial are equally encouraging."

Increased Coverage of the Putamen Observed in Cohort 3; Six-Month Efficacy Results Expected Mid-2017

The five patients enrolled in Cohort 3 received similar infusion volumes of VY-AADC01 compared to Cohort 2 (up to 900 µL per putamen), but three-fold higher vector genome concentrations, representing up to a three-fold higher total dose of up to 4.5×10^{12} vector genomes (vg) of VY-AADC01 compared to patients in Cohort 2 (1.5×10^{12} vg). Patients enrolled in Cohort 3 were similar in baseline characteristics to Cohort 1 and 2. The use of real-time, intra-operative MRI-guided delivery allowed the surgical teams to visualize the delivery of VY-AADC01 and continue to achieve greater average coverage of the putamen in Cohort 3 (42%) compared to Cohort 2 (34%) with similar infusion volumes and Cohort 1 (21%) with a lower infusion volume (Figure 1). The surgical procedure was successfully completed in all five patients. Infusions of VY-AADC01 have been well-tolerated with no vector-related serious adverse events (SAEs) or surgical complications in Cohort 3, and all five patients were discharged from the hospital within two days following surgery. The Phase 1b trial remains on track to deliver six-month safety, motor function, and biomarker data from Cohort 3, as well as longer-term safety and motor function data from Cohorts 1 and 2, in mid-2017.

Figure 1: Coverage of the Putamen with VY-AADC01 is available at

http://www.globenewswire.com/NewsRoom/AttachmentNg/5b657736-4f0d-4188-a295-b23eaee252f9

Correlation Data from Cohorts 1 and 2

Interim positive results from the Phase 1b trial from Cohorts 1 and 2 reported in early December 2016 demonstrated that VY-AADC01 dose-dependently improved measures of motor function and enhanced response to levodopa at six and twelve months and that administration of VY-AADC01 was well-tolerated (Figure 2). Since then, the Company has further analyzed the relationship between surgical coverage of the putamen with VY-AADC01 and enzyme activity of aromatic L-amino acid decarboxylase (AADC) that is responsible for converting levodopa to dopamine in the putamen using [^{18}F] fluorodopa (or F-Dopa) positron emission tomography (PET). The results demonstrate that surgical coverage of the putamen was highly correlated with change in AADC enzyme activity measured by F-Dopa PET ($r=0.81$, $p<0.05$).

Figure 2. Interim Phase 1b Results Strengthen Clinical Hypothesis

Biomarker/Motor Function Endpoint	**Result**
Dose-dependent *increase* in putaminal vector delivery and coverage	Cohort 1 (21%) vs. Cohort 2 (34%) [1]
Dose-dependent *increase* in putaminal AADC enzyme activity	Cohort 1 (13%) vs. Cohort 2 (56%) [1]
Dose-dependent, marked *decrease* in levodopa dose	Cohort 1 (10%) vs. Cohort 2 (35%) [2]
Dose-dependent and durable *improvement* in UPDRS-III on medication	Cohort 1 (1.6-point, 21% worsening) vs. Cohort 2 (9.6-point 56% improvement) [1,3]
Dose-dependent and durable *increase* in diary on-time	Cohort 1 (1.6 hours, 16%) vs. Cohort 2 (4.1 hours, 43%) [2]
Dose-dependent and durable *decrease* in diary off-time	Cohort 1 (1.4 hours, 27%) vs. Cohort 2 (2.2 hours, 48%) [2]

Source: Voyager Therapeutics press release issued December 8, 2016

1) Data at 6-months from baseline
2) Cohort 1 12-month data from 5/5 patients and Cohort 2 12-month data from 3/5 patients. 2/5 patients in Cohort 2 have not reached 12-month follow-up
3) Results reported at six months were maintained at 12 months

"In Cohorts 1 and 2 the increased coverage of the putamen with VY-AADC01 correlated nicely with increased AADC activity and this was associated with both dose-dependent and time-dependent improvements in multiple clinical measures of motor function in patients with advanced Parkinson's disease," added Steven Paul, M.D., president and chief executive officer of Voyager Therapeutics. "We believe these results support our therapeutic strategy of increasing putaminal dopamine levels with VY-AADC01 to enhance the response to oral levodopa and thus, we are pleased by the further increase in coverage observed in Cohort 3."

About the Phase 1b Trial of VY-AADC01 for Advanced Parkinson's Disease

In advanced Parkinson's disease, the putamen is depleted of dopamine and of the AADC enzyme that is responsible for converting levodopa to dopamine. VY-AADC01 is Voyager's gene therapy vector that contains the gene that encodes the AADC enzyme. The Phase 1b, open-label trial includes up to 20 patients with advanced Parkinson's disease and disabling motor fluctuations, treated with a single administration of VY-AADC01. The primary objective of the trial is to assess the safety and surgical coverage of ascending doses of VY-AADC01 in the putamen, a region of the brain associated with impaired motor function in Parkinson's disease. The secondary objectives of the trial include the assessment of AADC expression and activity in the putamen measured by F-Dopa PET. In addition, changes in motor responses to levodopa are measured by a controlled intravenous infusion of levodopa and by measuring daily requirements for levodopa and related medications. Other secondary objectives include assessment of motor function as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) and a patient-completed (Hauser) diary.

About Parkinson's Disease and VY-AADC01

Parkinson's disease is a chronic, progressive and debilitating neurodegenerative disease that affects approximately 700,000 people in the U.S. [1] and seven to 10 million people worldwide[2]. It is estimated that up to 15% of the prevalent population with Parkinson's disease, or approximately 100,000 patients in the U.S., have motor fluctuations that are refractory, or not well-controlled, with levodopa. While the underlying cause of Parkinson's disease in most patients is unknown, the motor symptoms of the disease arise from a loss of neurons in the midbrain that produce the neurotransmitter dopamine. Declining levels of dopamine in this particular region of the brain leads to the motor symptoms associated with Parkinson's disease including tremors, slow movement or loss of movement, rigidity, and postural instability. Motor symptoms during the advanced stages of the disease include falling, gait freezing, and difficulty with speech and swallowing, with patients often requiring the daily assistance of a caregiver.

There are currently no therapies that effectively slow or reverse the progression of Parkinson's disease. Levodopa remains the standard of care treatment, with its beneficial effects on symptom control having been discovered over 40 years ago[3]. Patients are generally well-controlled with oral levodopa in the early stages of the disease, but become less responsive to treatment as the disease progresses. Patients experience longer periods of reduced mobility and stiffness termed off-time, or the time when medication is no longer providing benefit, and shorter periods of on-time when their medication is effective.

The progressive motor symptoms of Parkinson's disease are largely due to the death of dopamine neurons in the substantia nigra, a part of the midbrain that converts levodopa to dopamine, in a single step catalyzed by the enzyme AADC. Neurons in the substantia nigra release dopamine into the putamen where the receptors for dopamine reside. In advanced Parkinson's disease, neurons in the substantia nigra degenerate and the enzyme AADC is markedly reduced in the putamen, which limits the brain's ability to convert oral levodopa to dopamine [4]. The intrinsic neurons in the putamen, however, do not degenerate in Parkinson's disease [5,6]. VY-AADC01, comprised of the adeno-associated virus-2 capsid and a cytomegalovirus promoter to drive AADC transgene expression, is designed to deliver the AADC gene directly into neurons of the putamen where dopamine receptors are located, bypassing the substantia nigra neurons and enabling the neurons of the putamen to express the AADC enzyme to convert levodopa into dopamine. The approach with VY-AADC01, therefore, has the potential to durably enhance the conversion of levodopa to dopamine and provide clinically meaningful improvements in motor symptoms following a single administration.

[1] Willis et al, *Neuroepidemiology*.2010;34:143–151
[2] www.pdf.org/en/parkinson_statistics
[3] Poewe W, et al, *Clinical Interventions in Aging*.2010;5:229-238.
[4] Lloyd, *J Pharmacol Exp Ther*. 1975;195:453-464, Nagatsu, *J Neural Transm Suppl*.2007
[5] Cold Spring Harb Perspect Med 2012;2:a009258
[6] Braak et al, *Cell Tissue Res*.2004;318:121-134

About Voyager Therapeutics

Voyager Therapeutics is a clinical-stage gene therapy company developing life-changing treatments for severe diseases of the CNS. Voyager is committed to advancing the field of adeno-associated virus (AAV) gene therapy through innovation and investment in vector engineering and optimization, manufacturing and dosing and delivery techniques. The Company's pipeline focuses on severe CNS diseases in need of effective new therapies, including advanced Parkinson's disease, a monogenic form of ALS, Friedreich's ataxia, Huntington's disease, frontotemporal dementia, Alzheimer's disease and severe, chronic pain. Voyager has broad strategic collaborations with Sanofi Genzyme, the specialty care global business unit of Sanofi, 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. For more information, please visit www.voyagertherapeutics.com. Follow Voyager on LinkedIn.

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 law. The use of words such as "may," "might," "will," "should," "expect," "plan," "anticipate," "believe," "estimate," "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 complete, clinical trials, its ability to continue to develop its product engine, its ability to add new programs to its pipeline, its expected cash, cash equivalents and marketable securities at the end of a fiscal year and anticipation for how long expected cash, cash equivalents and marketable securities will last, 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. These statements are also subject to a number of material risks and uncertainties that are described in Voyager's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission, as updated by its future 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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