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

12/07/16

VY-AADC01 dose-dependently improved measures of motor function and enhanced response to levodopa at six and twelve months; administration of VY-AADC01 was well-tolerated

Program on track to report Cohort 3 data mid-2017 and to begin placebo-controlled trial Q4:17

Conference call scheduled for today at 4:30 p.m. EST

CAMBRIDGE, Mass., Dec. 07, 2016 (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 positive results from the ongoing Phase 1b trial of VY-AADC01 at six and twelve months of follow-up in patients with advanced Parkinson's disease. The interim data from Cohorts 1 and 2 of this trial demonstrated that accurate MRI-guided delivery of escalating doses of VY-AADC01 were well tolerated and resulted in increased coverage of the putamen, increased AADC enzyme activity, enhanced response to levodopa, and dose-related, clinically meaningful improvements in various measures of patients' motor function. This was especially evident at the higher dose in Cohort 2 with improved UPDRS off medication and on medication scores, and corresponding improvements in patient-reported diary hours, suggesting higher peak effects and a longer duration of action of levodopa. These effects were maintained and in some patients improved at 12 months of follow-up.

"At 12 months in Cohort 2, treatment with VY-AADC01 resulted in a 14-point, or 44%, improvement in UPDRS-III off medication, a 9-point, or 55% improvement in UPDRS-III on medication, and a 2.2 hour, or 48%, decrease in diary off-time from baseline," said Bernard Ravina, M.D., M.S., vice president of clinical development at Voyager Therapeutics. "Very importantly, these improvements in motor function occurred with a substantial 34% reduction in daily doses of oral levodopa and related medications at six months in Cohort 2 that was maintained at 12 months, a magnitude that we find compelling and consistent with the mechanism of action of VY-AADC01. The dose-escalating portion of this trial continues and we plan to complete Cohort 3 enrollment in early 2017, report 6-month data from this Cohort as well as longer-term data from Cohorts 1 and 2 in mid-2017, and present results from this trial at a medical conference in the first half of next year."

About the Phase 1b Trial

In advanced Parkinson's disease, the putamen is depleted of dopamine and of the enzyme aromatic L-amino acid decarboxylase (AADC) 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 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 positron emission tomography (PET) using [^{18}F] fluorodopa (or ^{18}F-DOPA). 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.

The UPDRS is a standard clinical rating scale for Parkinson's disease. Part III of this scale measures motor function by physician examination. The UPDRS is conducted when patients are taking their Parkinson's disease medications (referred to as "on" medication) and when patients are not taking their Parkinson's disease medications (referred to as "off" medication). In the patient-completed diary, patients record their motor response over the course of several days as on-time, or time when they have good mobility with or without non-troublesome dyskinesia, off-time when they have poor mobility, and on-time with troublesome dyskinesia when they have uncontrolled movements.

Biomarker and Clinical Results Summary

Today's interim results include data from all 10 patients treated in Cohorts 1 and 2 at six months (five patients in each Cohort), and where indicated, data from five patients in Cohort 1 and three patients in Cohort 2 who have reached 12 months of follow-up. Patients in Cohorts 1 and 2 received a single administration of VY-AADC01 at a total dose of up to 7.5×10^{11} vector genomes (vg) and 1.5×10^{12} vg, respectively. Patients enrolled in Cohorts 1 and 2 were on average 58 years of age with a Parkinson's disease diagnosis for an average of 10 years. Patients were candidates for surgical intervention due to disabling motor complications despite treatment with optimal anti-Parkinsonian medication. At baseline, the average UPDRS III off medication score was 37.2 and 35.8, and the average patient diary off-time was 4.9 and 4.2 hours, for Cohort 1 and 2, respectively. Patients' average amount of Parkinson's disease medications at baseline was 1,468 mg per day for Cohort 1 and 1,636 mg per day for Cohort 2. The results below are reported as mean changes from baseline to six months, or 12 months where indicated.

Putamen Coverage and Biomarker Data

- The use of real-time, intra-operative MRI-guided delivery and increasing infusion volumes resulted in 21% coverage of the volume of the putamen with VY-AADC01 in Cohort 1 and 34% coverage in Cohort 2.
- VY-AADC01 treatment resulted in a 13% increase in putaminal AADC enzyme activity in Cohort 1 and a 56% increase in putaminal AADC enzyme activity in Cohort 2 at six months relative to baseline as measured by ^{18}F-DOPA PET scans.
- Patients reduced their daily oral dose of levodopa and related medications by 14% in Cohort 1 and 34% in Cohort 2 at six

months. This reduction in oral medication was generally maintained at twelve months.

- VY-AADC01 treatment prolonged the duration and markedly increased the motor symptom response to levodopa measured following a controlled intravenous infusion of levodopa administered six months after surgery when compared to baseline.

Clinical Data Summary

Treatment with VY-AADC01 resulted in the following:

- 15.6-point and 17.8-point (42% and 50%) improvement (reduction) in UPDRS-III off medication at six months in Cohort 1 and Cohort 2, respectively. These improvements were 16.4-point and 14.3-point (44% and 44%) for Cohorts 1 and 2, respectively, at 12 months.

- 9.6-point (56%) improvement (reduction) in UPDRS-III on medication in Cohort 2 at six months that was sustained at 12 months. Cohort 1 demonstrated a 1.6-point (21%) worsening (increase) at six months that was sustained at 12 months.

- 2.2 hours (20%) increase in diary on-time (with no dyskinesias or non-troublesome dyskinesias) in Cohort 2 at six months that further increased to 4.1 hours (43%) at 12 months. Cohort 1 showed a slight decrease in on-time at six months of 0.3 hours (-3%) and an increase of 1.6 hours (16%) at 12 months.

- 1.1 hour (27%) decrease in diary off-time in Cohort 2 at six months that further decreased to 2.2 hours (48%) at 12 months. Decreases in diary off-time in Cohort 2 also occurred in conjunction with a reduction in troublesome dyskinesias. Cohort 1 showed a decrease in diary off-time of 0.8 hours (16%) at six months and 1.4 hours (27%) at 12 months.

Safety Data from Cohorts 1 and 2

The surgical procedure was successfully completed in all 10 patients and infusions of VY-AADC01 have been well-tolerated with no vector-related serious adverse events (SAEs). Nine of the 10 patients were discharged from the hospital within one to two days following surgery. As previously reported, one patient experienced two SAEs; a pulmonary embolism or blood clot in the lungs, and related heart arrhythmia or irregular heartbeat. The patient was treated with an anti-coagulant and symptoms associated with the SAEs have completely resolved. Investigators determined that this was most likely related to immobility during the surgical procedure and subsequent formation of a blood clot, or deep vein thrombosis (DVT), in the lower extremity. Consequently, DVT prophylaxis was added to the surgical protocol and no subsequent events have been observed following implementation of these measures.

"Our surgical experience with VY-AADC01 and the results to date show that MRI-guided infusions are well tolerated and substantially improve our ability to tailor the infusions to fit the patients' anatomy and accurately deliver vector to the putamen," said Paul Larson, M.D., Professor and Vice Chair of Clinical Neurological Surgery, University of California San Francisco, and investigator in the trial. "The increased surgical coverage of the putamen is further validated by the PET data and is translating into motor function improvement in patients with advanced stages of the disease."

Todd Sherer, Ph.D., Chief Executive Officer, The Michael J. Fox Foundation for Parkinson's Research added, "Levodopa has been the gold-standard treatment for Parkinson's for decades, but it has limitations. Enhancing a patient's response to this therapy represents an important development for those who suffer from the advanced stages of this disease, and we are glad to see the continued progress of this program." The Michael J. Fox Foundation funded part of the initial pioneering research for this program in Dr. Krystof Bankiewicz's laboratory at the University of California San Francisco.

Cohort 3 and Posterior Trajectory Trial On Track

To advance the planned dose-escalating portion of the trial, Voyager continues to enroll patients in Cohort 3 (up to five patients) who will receive a single administration of VY-AADC01 at a total dose of up to 4.5×10^{12} vector genomes (vg), representing a three-fold higher total dose than patients in Cohort 2 (1.5×10^{12} vg). To date, four of five patients have been treated in Cohort 3 and Voyager plans to complete Cohort 3 enrollment in early 2017 and remains on track to report six-month data in mid-2017. In preparation for the randomized, placebo-controlled trial, Voyager also plans to initiate a new trial that could enhance the efficiency of the surgical delivery and further increase both coverage and total vector dose. This trial will employ a posterior (i.e., back of the head), or occipital, trajectory which aligns the infusion of VY-AADC01 with the anatomical structure of the putamen. Voyager believes this will result in a higher total volume of coverage of the putamen and therefore a higher total dose (up to 9.4×10^{12} vg, representing a two-fold higher total dose than patients in Cohort 3) and may reduce surgical times. Voyager is activating additional clinical trial sites this quarter and plans to dose the first patient with this trajectory in the first quarter of 2017. Data from Cohorts 1-3 and from this posterior trajectory trial will inform the design of the placebo-controlled trial planned to begin in the fourth quarter of 2017.

Conference Call and Webcast Information

Voyager will host a conference call and webcast today with slides at 4:30 p.m. EST to discuss the results. The conference call may be accessed by dialing (877) 851-3834 for domestic callers or +1 (631) 291-4595 for international callers, and referencing conference ID number 32331935. A live audio webcast of the conference call and replay will be available online from the Investors & Media section of Voyager's website at www.voyagertherapeutics.com. The webcast will be archived for 30 days.

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 aromatic L-amino acid decarboxylase (AADC) enzyme. 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 neurons in the putamen 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 the putamen where the 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.

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.

[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

Investor Relations:
Matt Osborne
Head of Investor Relations & Corporate Communications
857-259-5353
mosborne@vygr.com

Media:
Katie Engleman
Pure Communications, Inc.
910-509-3977
Katie@purecommunicationsinc.com

Voyager Therapeutics