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

September 6, 2017

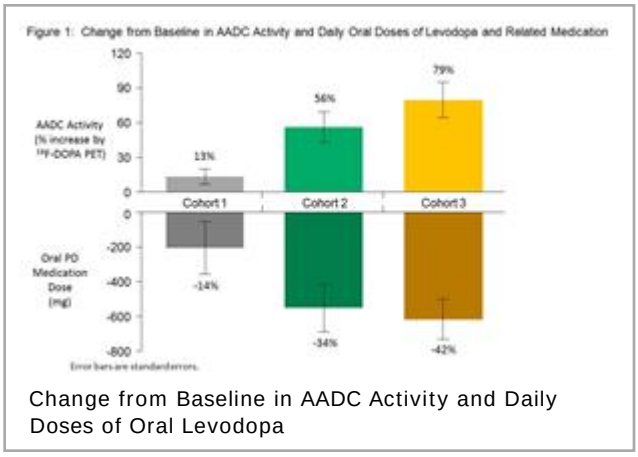
VY-AADC01 improved multiple measures of patients' motor function and activities of daily living in Cohorts 2 and 3

Robust and durable clinical effects achieved with substantial reductions in daily oral levodopa use and other Parkinson's medications; one-time administrations of VY-AADC01 well-tolerated out to 24 months

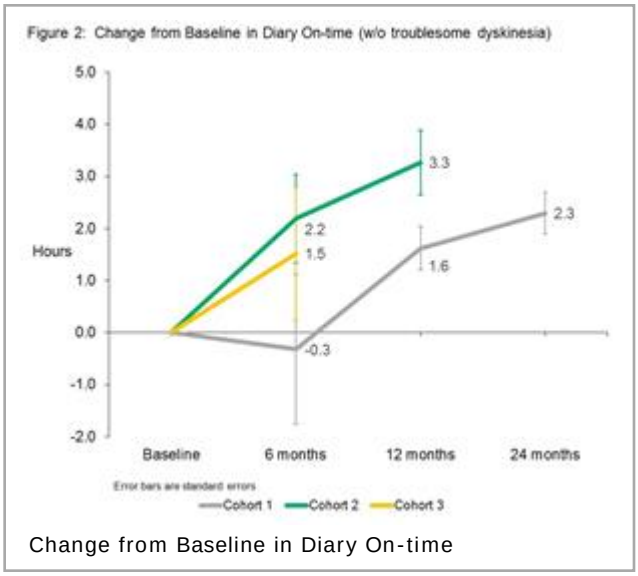
Pivotal Phase 2-3 program on track to begin during late 2017 and to dose the first patient during the first half of 2018

Conference call scheduled for today at 8:00 a.m. EDT

CAMBRIDGE, Mass., Sept. 06, 2017 (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 positive results from its ongoing Phase 1b trial of VY-AADC01 in advanced Parkinson's disease. The results demonstrated durable, dose-dependent and time-dependent improvements across multiple measures of patients' motor function after a one-time administration of the gene therapy. These measures include patient-reported diaries, Parkinson's disease rating scales, and activities of daily living.



Change from Baseline in AADC Activity and Daily Doses of Oral Levodopa



Change from Baseline in Diary On-time

"We are very pleased with the updated results from our dose-escalation trial. By six months in Cohort 3, patients achieved the clinically meaningful improvements in motor symptoms that were observed in Cohort 2 and with even lower doses of their oral Parkinson's medications, including levodopa," said Bernard Ravina, M.D., M.S., chief medical officer of Voyager Therapeutics. "These data suggest that higher doses of VY-AADC01 result in greater AADC activity, increasing the patient's capacity to produce dopamine and, therefore, reducing their need for oral Parkinson's medications. As a result, patients in the trial are spending more time during the day with good motor function, less time with poor motor function, and are experiencing less disability. For patients in Cohort 2 at 12 months, this meant an average increase during the day of four hours of on-time without dyskinesia, which is a very meaningful change. We believe the distinct mechanism of action of VY-AADC01 that allows patients to achieve this motor function improvement while markedly reducing their Parkinson's medications to this extent and duration reflects a pattern that has not been seen in previous Parkinson's gene therapy trials and does not exist with current or emerging treatments."

Steven Paul, M.D., Voyager's president and chief executive officer added, "These encouraging results continue to de-risk the program and support the use of either dose of VY-AADC01 administered in Cohort 2 or Cohort 3 for our planned pivotal trial. We continue to be impressed with the Cohort 2 data out to 12 months, namely, the increase in diary on-time of four hours without dyskinesia, decrease in off-time of 54%, supported by a 56% reduction in UPDRS-III motor scores while on medication. In addition, preliminary results from our posterior delivery trial suggest that even greater coverage of the putamen, the brain region we are targeting, can be achieved and with shorter administration times. We are excited to continue to follow the patients in this Phase 1b trial, particularly patients in Cohort 3 from six to 12 months, and those in the posterior delivery trial, as we approach the start of the pivotal Phase 2-3 program later this year."

About the Phase 1b Trial

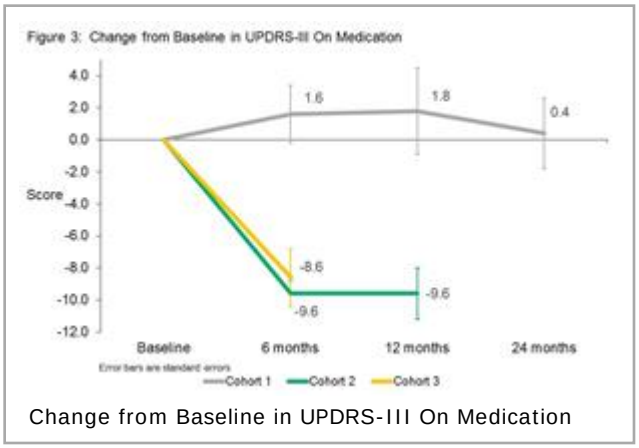
In advanced Parkinson's disease, the putamen is depleted of dopamine and of the enzyme aromatic L-amino acid decarboxylase (AADC) that is responsible

for converting levodopa to dopamine. VY-AADC01 is Voyager's gene therapy vector that contains the gene that encodes the AADC enzyme. A single administration of VY-AADC01 into the putamen could offer advanced patients' improved motor function while reducing their requirements for oral levodopa and other dopaminergic medications and their associated behavioral and motor side effects.

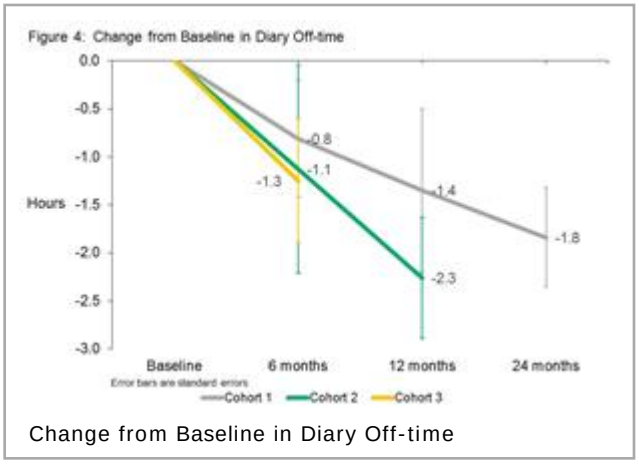
- The Phase 1b, open-label trial includes 15 patients with advanced Parkinson's disease and disabling motor fluctuations, treated with a single administration of VY-AADC01.

- The primary objective of the trial is to assess the safety and distribution of ascending doses of VY-AADC01 administered under magnetic resonance imaging (MRI) guidance to the putamen, a region of the brain associated with impaired motor function in Parkinson's disease.

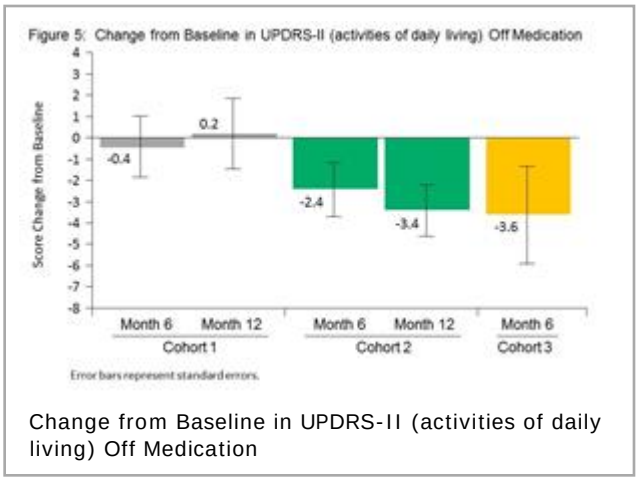
- Secondary objectives include assessment of AADC expression and activity in the putamen measured by positron emission tomography (PET) using [^{18}F] fluorodopa (or ^{18}F-DOPA), which reflects the capacity to convert levodopa to dopamine. Other secondary measures include assessments of motor function and activities of daily living, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS-III and UPDRS-II, respectively), quality of life, and a patient-completed (Hauser) diary. Daily requirements for levodopa and related medications are also measured.



Change from Baseline in UPDRS-III On Medication



Change from Baseline in Diary Off-time



Change from Baseline in UPDRS-II (activities of daily living) Off Medication

Biomarker and Clinical Results Summary

Today's interim results include data from all 15 patients treated in Cohorts 1, 2 and 3 (five patients in each Cohort) including data from patients in Cohort 1 at 24 months, Cohort 2 at 12 months and Cohort 3 at six months. 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. This volume and concentration for Cohort 3 represents 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 who received a total dose of up to 1.5×10^{12} vg. Patients in Cohort 1 received lower volumes (up to 450 µL per putamen) and lower vector genome concentrations for at a total dose of up to 7.5×10^{11} vg.

Patients enrolled in Cohorts 1, 2 and 3 were:

- On average, 58 years of age with a Parkinson's disease diagnosis for an average of 10 years.

- Candidates for surgical intervention including deep-brain stimulation due to disabling motor complications despite treatment with optimal anti-Parkinsonian medication.

- At baseline, the average patient diary on-time without troublesome dyskinesia was 10.5 hours, average UPDRS-III on medication score was 13.5, average diary off-time was 4.6 hours and average UPDRS-II activities of daily living off medication score was 16.5.

- At baseline, patients were treated with maximal levels of multiple dopaminergic medications including, in many cases, amantadine for the treatment of dyskinesia, or uncontrolled or involuntary movements. Patients' average amount of Parkinson's disease medications at baseline was 1,526 mg of oral levodopa equivalents per day.

Putamen Coverage, AADC Activity and Daily Doses of Oral Levodopa

- The use of real-time, MRI-guided delivery and increasing infusion volumes resulted in 21% mean coverage of the volume of the putamen with VY-AADC01 in Cohort 1, 34% mean coverage in Cohort 2, and 42% mean coverage in Cohort 3.

- VY-AADC01 treatment resulted in a 13% increase, a 56% increase, and a 79% increase in mean putaminal AADC enzyme activity in Cohort 1, 2, and 3, respectively at six months relative to baseline as measured by ^{18}F-DOPA PET scans (Figure 1). Coverage of the putamen and AADC enzyme activity were highly correlated (r=0.84, p=0.0002)

- VY-AADC01 treatment resulted in reduced daily doses of oral levodopa and related medications to achieve optimal motor control, suggesting a greater capacity for patients to make more dopamine but with less need for oral levodopa. Patients' Parkinson's medications were reduced by a mean of 208 mg (14%), 553 mg (34%) and 618 mg (42%) for Cohorts 1, 2 and 3, respectively, at six months compared with baseline (Figure 1).

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Clinical Motor Function, Activities of Daily Living Data Summary

Treatment with VY-AADC01 resulted in dose-dependent (Cohorts 2 and 3 versus Cohort 1) and time-dependent clinically meaningful improvements in patients' motor function in diary on-time without troublesome dyskinesia (Figure 2). This included an increase in diary on-time without dyskinesia of 4.0 hours from baseline to 12 months for patients in Cohort 2 and a reduction in patients' on-time with troublesome dyskinesia (data not shown in Figure 2).

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Scores for UPDRS-III, the physician-rated motor examination, also improved (reduced scores) while patients were on their medication in a dose-related manner (Cohorts 2 and 3 versus Cohort 1). These changes in self-reported diary on-time and UPDRS-III on medication are consistent with an enhanced response to oral levodopa and related medications (Figure 3).

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In addition, VY-AADC01 reduced patients' off-time as self-reported by diary (Figure 4).

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VY-AADC01 demonstrated dose-dependent and time-dependent improvements in patients' activities of daily living as measured by reductions in the UPDRS-II off medication score, including a change in mean score from baseline of -2.4 for Cohort 2 at 6 months compared with a change in score from baseline of -3.6 for Cohort 3 at 6 months (Figure 5).

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Safety Data from Cohorts 1, 2 and 3

The infusion was successfully completed in all 15 patients and infusions of VY-AADC01 have been well-tolerated with no vector-related serious adverse events (SAEs). Fourteen of the 15 patients were discharged from the hospital within 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 administration and subsequent formation of a blood clot, or deep vein thrombosis (DVT), in the lower extremity. Consequently, DVT prophylaxis was added to the protocol and no subsequent events have been observed.

Phase 1b Posterior Trajectory Trial Completes Additional Patient Dosing

Investigators recently completed dosing additional patients in a separate Phase 1 trial designed to further optimize the intracranial delivery of VY-AADC01. This planned Phase 1 trial explores a posterior, or back of the head, delivery approach, compared to Cohorts 1 through 3 from the ongoing Phase 1b trial that used a transfrontal, or top of the head, delivery approach into the putamen. A posterior approach better aligns the infusion of VY-AADC01 with the anatomical structure of the putamen to potentially reduce the total procedure time and increase the total coverage of the putamen.

Administration of VY-AADC01 with this posterior approach was well-tolerated by the three patients dosed since the start of the trial. No serious adverse events were reported, and patients were discharged from the hospital the day after surgery. The posterior approach resulted in greater average putaminal coverage (approximately 50%) and reduced average administration times compared with the transfrontal approach of Cohorts 1 through 3. Voyager continues to expect to enroll more patients in this trial prior to the start of the pivotal Phase 2-3 program.

Pivotal Phase 2-3 Program on Track to Begin During Late 2017

Voyager remains on track to begin the pivotal Phase 2-3 program for VY-AADC01 late this year and dose the first patient during the first half of 2018. The company will continue to follow patients from Cohorts 1 through 3, and those in the posterior trajectory trial, and plans to report updated results from these trials during the first quarter of 2018, prior to the start of patient enrollment in the pivotal program.

Conference Call Information

Voyager will host a conference call and webcast today at 8:00 a.m. EDT. The live 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 80581781. A live audio webcast of the conference call 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-AADC

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 region of the brain, the putamen, 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-AADC, 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-AADC, therefore, has the potential to durably enhance the conversion of levodopa to dopamine and provide clinically meaningful improvements by restoring motor function in patients and improving symptoms following a single administration.

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 adeno-associated virus (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 advanced Parkinson's disease, a monogenic form of ALS, Huntington's disease, Friedreich's ataxia, 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.

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," "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 product engine; its ability to add new programs to its pipeline; its ability to enter into new partnerships or collaborations; its expected cash, cash equivalents and marketable debt securities at the end of a fiscal year and anticipation for how long expected cash, cash equivalents and marketable debt 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. Such risks and uncertainties include, among others, those related to the initiation and conduct of preclinical studies and clinical trials, the availability of data from clinical trials and the expectations for regulatory submissions and approvals; the continued development of the product engine; Voyager's scientific approach and general development progress; the availability or commercial potential of Voyager's product candidates; the sufficiency of cash resources; and need for additional financing. 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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[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

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