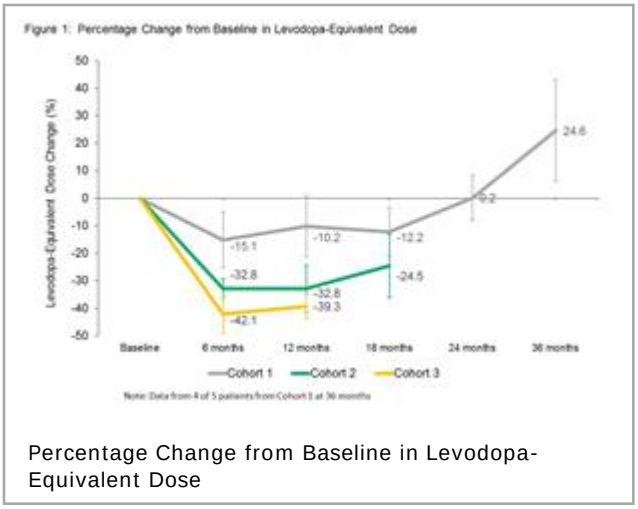
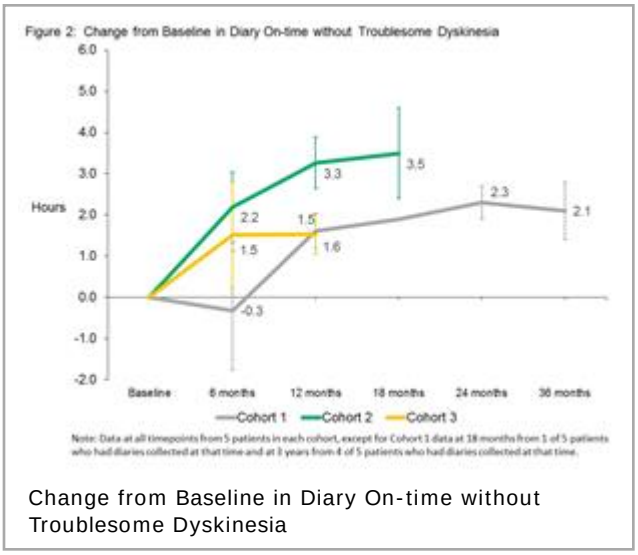
Voyager Therapeutics Announces Longer-Term Data from Ongoing Phase 1b Trial of VY-AADC for Advanced Parkinson's Disease

March 9, 2018

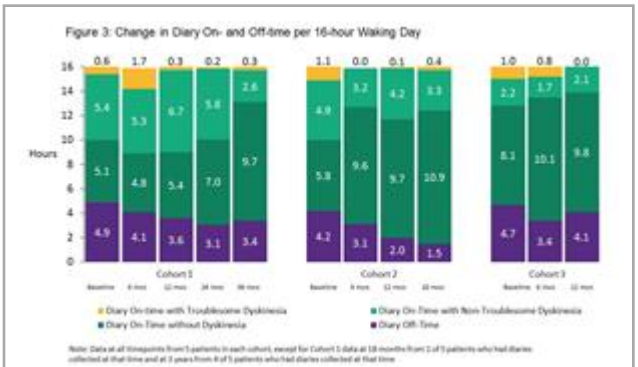
Robust and durable improvements in patients' motor function achieved with substantial reductions in use of daily oral levodopa and other Parkinson's disease medications; one-time administrations of VY-AADC well-tolerated now out to three years in Cohort 1



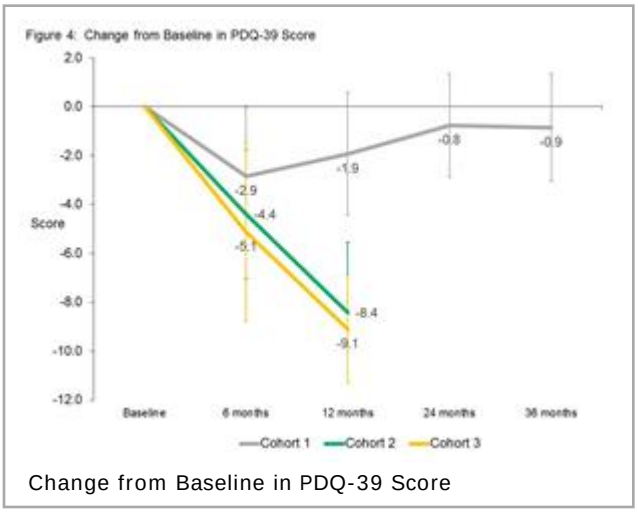
Percentage Change from Baseline in Levodopa-Equivalent Dose



Change from Baseline in Diary On-time without Troublesome Dyskinesia



Change in Diary On- and Off-time per 16-hour Waking Day



Change from Baseline in PDQ-39 Score

In Cohort 2 at 18 months, patients had a mean increase of five hours a day of on-time without any dyskinesia and experienced 65% less off-time, making this the likely dose for the pivotal Phase 2-3 program that remains on track to dose the first patient mid-2018

Conference call scheduled for today at 8:30 a.m. EST

CAMBRIDGE, Mass., March 09, 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 longer-term data from its ongoing dose-ranging Phase 1b trial of VY-AADC in advanced Parkinson's disease. The results continue to demonstrate 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 quality of life, with diary on-time without troublesome dyskinesia at twelve months as the proposed primary endpoint of the planned pivotal program. The update of results from the ongoing Phase 1b trial of VY-AADC include a durable 2.1-hour improvement in patient-reported diary on-time without troublesome dyskinesia from baseline to three years for patients in Cohort 1, a durable and clinically meaningful 3.5-hour improvement from baseline to 18 months in Cohort 2, and an improvement from baseline to six months of 1.5 hours that plateaued from six to 12 months in Cohort 3.

"We continue to be pleased with the duration and magnitude of effect of VY-AADC on multiple measures of patients' motor function and quality of life, which is consistent with the mechanism of action of VY-AADC suggesting a greater capacity for patients to make more dopamine and improve their motor function with less need for oral levodopa," said Bernard Ravina, M.D., M.S., chief medical officer of Voyager Therapeutics. "In our dose-ranging Phase 1b trial, we systematically increased the dose of VY-AADC to select an optimal dose prior to initiating our pivotal program. We believe we have achieved this with our Cohort 2 dose, in which patients increased their on-time without any dyskinesia by five hours at 18 months and reduced their off-time by more than 60%. Not unexpectedly, our Cohort 3 dose resulted in greater rates of levodopa-induced dyskinesia that resolved with marked reductions in patients' oral levodopa and related medicines but resulted in less robust control of motor function compared to Cohort 2 by 12 months. Given the improvements in motor function and wider spectrum to titrate oral levodopa with our Cohort 2 dose, we are excited to consider this as our likely dose in the pivotal program while still planning to review the six-month results from the Phase 1 posterior trajectory trial next quarter. We look forward to reviewing these results from the Phase 1b with the FDA as part of a planned Type C meeting and we continue to expect to dose the first patient in the pivotal Phase 2-3 program in mid-2018."

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-AADC is Voyager's gene therapy vector that contains the gene that encodes the AADC enzyme. A single administration of VY-AADC into the putamen could offer advanced patients improvements in motor function while reducing their requirements for oral levodopa and other dopaminergic medications and 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-AADC.

- The primary objectives of the trial are to assess the safety and tolerability of VY-AADC and to test the distribution of ascending doses of VY-AADC 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.

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 three years, Cohort 2 at 18 months and Cohort 3 at one year. Patients enrolled in Cohort 3 received similar infusion volumes of VY-AADC delivered with the transfrontal, or top of the head, approach compared to Cohort 2 (up to 900 µL per putamen), but three-fold higher vector genome (vg) concentrations. This volume and concentration for Cohort 3 represents up to a three-fold higher total dose of up to 4.5×10^{12} vg of VY-AADC 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 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. Patients in Cohort 3 entered the trial with approximately 50% more severe dyskinesia at baseline than patients in Cohorts 1 and 2 based on the Unified Dyskinesia Rating Scale, with a mean score of 30.2 for Cohort 3 compared with a mean score of 19.2 and 17.4 for Cohorts 1 and 2, respectively.

- 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.

- During the trial, patients were instructed to reduce their daily doses of oral levodopa and related medications, or levodopa equivalent doses (LEDs), to achieve optimal motor control in response to severe dyskinesia observed post-treatment with VY-AADC. In this trial, patients' Parkinson's disease LEDs were reduced by a mean of 15%, 33% and 42% for Cohorts 1, 2 and 3, respectively, from baseline to six months. LED reductions were sustained for Cohorts 1 and 2 to eighteen months and for Cohort 3 to 12 months (Figure 1).

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Clinical Motor Function Data Summary

Treatment with VY-AADC resulted in a durable 2.1-hour improvement in patient-reported diary on-time without troublesome dyskinesia from baseline to three years for patients in Cohort 1, a durable and clinically meaningful 3.5-hour improvement from baseline to 18 months in Cohort 2, and an improvement from baseline to six months of 1.5 hours that plateaued from six to 12 months in Cohort 3 (Figure 2). Cohort 3 patients had higher levels of severe dyskinesia at baseline than patients in Cohorts 1 and 2. This, coupled with treatment with a higher dose of VY-AADC, resulted in patients in Cohort 3 reducing their LEDs to a greater extent than patients in Cohorts 1 and 2 and may have resulted in less robust control of motor function as measured by on-time without troublesome dyskinesia compared to Cohort 2 by 12 months. Voyager intends to apply these learnings to the protocols for the pivotal Phase 2-3 program.

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VY-AADC also generated durable improvements in this trial in other measures of motor function including decreases in both diary off-time and diary on-time with troublesome dyskinesia and increases in both diary on-time without dyskinesia and diary on-time with non-troublesome dyskinesia. In Cohort 2 at 18 months, patients had a mean increase of 5.1 hours a day of on-time without any dyskinesia and experienced 65% less off-time (Figure

3).

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In addition to motor function, VY-AADC improved patients' quality of life as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) Part II activities of daily living section and the patient-reported 39-item Parkinson's Disease Questionnaire (PDQ-39), demonstrating dose-dependent and clinically meaningful improvements in these scores. For PDQ-39, VY-AADC improved (reduced) patients' score by a mean change from baseline to 12 months of -8.4 and -9.1 for Cohorts 2 and 3, respectively (Figure 4).

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Safety Data from Cohorts 1, 2 and 3

Infusions of VY-AADC have been well-tolerated in all fifteen patients treated in these Cohorts 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.

Pivotal Phase 2-3 Program on Track to Begin Dosing Patients in Mid-2018

Voyager plans to meet with the Food and Drug Administration (FDA) during a Type C meeting to discuss the current Phase 1b data and designs for the pivotal program. Voyager expects to include information from this meeting, as well as data from Cohorts 1, 2 and 3 and the Phase 1 posterior trajectory trial, into the final design of the Phase 2-3 pivotal program, which remains on track to dose the first patient during mid-2018.

Conference Call Information

Voyager will host a conference call and webcast today at 8:30 a.m. EST. 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 8774548. 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 1,000,000 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 150,000 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 patients suffering from 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. The company'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, 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 Biotechnology Ltd, a division of AbbVie Inc., 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 perform under existing collaborations with, among others, Sanofi Genzyme and AbbVie and 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.

[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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