



Voyager Therapeutics Receives FDA Guidance on Development Path for VY-AADC for Parkinson's Disease and Provides Clinical Update

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Voyager continues to plan to submit a BLA for VY-AADC based on its pivotal program and Type C meeting feedback

Positive interim results with VY-AADC from the Phase 1 posterior trajectory trial supports the surgical approach and dose selection for the pivotal program

CAMBRIDGE, Mass., July 17, 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 feedback from a Type C meeting with the U.S. Food and Drug Administration (FDA). Based on the written response from the FDA, Voyager continues to plan to submit for review a biologics license application (BLA) for VY-AADC based on the nonclinical and clinical safety and efficacy data from the pivotal program, including plans to submit a BLA based on data from the randomized, placebo-controlled Phase 2 trial alone, or if needed, from the randomized, placebo-controlled Phase 3 trial.

In addition, Voyager today announced positive interim results from a Phase 1 posterior trajectory trial that achieved enhanced coverage of the putamen, reduced surgical times, and improvements in patients' motor function at six months that were consistent with improvements achieved from patients in Cohorts 2 and 3 at the same time point in Voyager's Phase 1b trial with VY-AADC. As a result, Voyager has determined that the posterior approach will continue to serve as the preferred surgical route of administration and that the pivotal program will use a dose concentration of VY-AADC between those used in Cohorts 2 and 3 from the Phase 1b trial.

"We are very pleased with feedback from the FDA regarding our pivotal program for VY-AADC that includes the potential to file a BLA based on the safety and efficacy results from the Phase 2 trial, or if needed, from the Phase 3 trial," said Robert Pietrusko, Pharm.D., senior vice president of regulatory affairs and quality assurance at Voyager. "With the recent RMAT designation for VY-AADC and written feedback from the FDA regarding our Type C meeting questions, we look forward to continuing to work closely with the agency to expedite the development of this potentially important treatment for patients with Parkinson's disease."

"Our VY-AADC program is progressing nicely and our plans are now further informed by this Type C regulatory feedback," said Andre Turenne, president and chief executive officer of Voyager. "We appreciate the agency's guidance and look forward to incorporating their feedback as we advance into our pivotal program. Importantly, the data from the posterior trajectory trial supports the results from Cohorts 2 and 3 from the Phase 1b trial and informs our selection of a dose concentration and route of delivery for our pivotal program."

Highlights from Type C meeting feedback from FDA

Voyager recently submitted questions to the FDA in preparation for a planned Type C meeting to discuss the regulatory pathway for VY-AADC for the treatment of Parkinson's disease in patients with motor fluctuations that are refractory to medical management. The purpose of the Type C meeting was to request feedback on the design of Voyager's planned pivotal program for VY-AADC that includes a Phase 2 and Phase 3 trial conducted in staggered parallel initiation and the potential to submit for review a BLA based on the nonclinical results and clinical results from this planned pivotal program.

The FDA indicated in a written response to Voyager that the Phase 2 randomized, placebo-controlled trial in approximately 42 patients, if it were to meet its primary endpoint of demonstrating a statistically-significant difference of diary on-time without troublesome dyskinesia compared to the placebo surgery group and in the absence of major safety concerns, likely may be considered sufficient for acceptance of submission for review of a BLA. The agency also indicated that if the results of the Phase 2 trial were supportive only and did not achieve the primary endpoint, the randomized, placebo-controlled Phase 3 trial in approximately 120 patients, if it were to achieve the primary endpoint and in the absence of major safety concerns, also likely may be considered sufficient for acceptance of submission for review of a BLA. Voyager also submitted questions to the agency regarding chemistry, manufacturing and controls (CMC) and nonclinical information for VY-AADC. Voyager believes that the written responses from the agency to these questions were informative and can be addressed to support the submission of a BLA for review.

Preliminary data from the Phase 1 posterior trajectory trial and data from the prior Phase 1b trial with VY-AADC supports the surgical approach and dose selection for the pivotal program for Parkinson's disease

Investigators successfully dosed eight patients with VY-AADC in a Phase 1 trial in patients with Parkinson's disease exploring the posterior (i.e., back of the head) infusion trajectory of VY-AADC and using the same dose concentration to patients in Cohort 3 from the Phase 1b trial. The posterior trajectory better aligns the infusion of VY-AADC with the anatomical structure of the putamen. As previously reported from all eight patients, this trajectory resulted in a greater average coverage of the putamen (approximately 50%) and reduced the total procedure time by two to three hours compared to Cohorts 1, 2 and 3 from the Phase 1b trial that employed a transfrontal, or top of the head, delivery approach into the putamen. In all eight patients, treatment with VY-AADC has been well-tolerated and no serious adverse events have been reported to date.

Today's update includes interim biomarker and motor function data from four of eight patients who have completed their motor function assessments at six months. On average, patient characteristics at baseline in this trial were consistent with patients in the Phase 1b trial, namely, patients on average were 57 years of age with a Parkinson's disease diagnosis for an average of nine years and all were candidates for surgical intervention including

deep-brain stimulation due to disabling motor complications despite treatment with optimal anti-Parkinsonian medication.

From baseline to six months, treatment with VY-AADC increased AADC enzyme activity in the putamen as measured by positron emission tomography (PET) using [18F] fluorodopa (or 18F-DOPA), which reflects the capacity of neurons in the brain to convert levodopa to dopamine. The increase in AADC enzyme activity in this trial was consistent with increases in AADC enzyme activity observed from patients in Cohort 3 from the Phase 1b trial.

Treatment with VY-AADC improved patients' motor function from baseline to six months across multiple assessments in a clinically-meaningful manner and consistent with results from Cohorts 2 and 3 from the Phase 1b trial during the same period of time. These assessments include patient self-reported diaries, both on- and off-times and diary on-time without troublesome dyskinesia, Unified Parkinson's Disease Rating Scales, and activities of daily living measures. In addition, improvements in patients' motor function using the posterior trajectory approach were observed with significant reductions in patients' oral levodopa and equivalent medications, similar to results observed from Cohorts 2 and 3 from the Phase 1b trial. Voyager plans to present data from the full cohort of eight patients from the Phase 1 posterior trajectory trial at future scientific and medical conferences.

Based on the safety, coverage of the putamen, PET imaging data, and reduced surgical times from the eight patients treated in this trial, the posterior approach will serve as the preferred infusion trajectory for the Phase 2 and 3 trials. In addition, based on results from the 15 patients treated in Cohorts 1, 2 and 3 from the Phase 1b trial and the eight patients dosed in the Phase 1 posterior trajectory trial including the four of eight patients who have completed their motor function assessments at six months, Voyager has chosen a dose concentration of VY-AADC for the pivotal program that is between the dose concentrations of Cohorts 2 and 3 from the Phase 1b trial.

Twenty-four clinical trial sites (including neurosurgical and neurology patient referral sites) have been selected for participation in the Phase 2 trial with institutional review board submission and site activation underway. During the remainder of the year, Voyager plans to provide updates as to the enrollment status of this trial.

For more information about Voyager's Phase 2 clinical trial with its gene therapy program VY-AADC for the treatment of Parkinson's disease, please use the following link:

<https://clinicaltrials.gov/ct2/results?cond=&term=+NCT03562494&cntry=&state=&city=&dist>

For additional information regarding this Phase 2 clinical trial, please email Voyager at: clinicaltrials@vygr.com.

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 worldwide². 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 ago³. 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 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 dopamine⁴. 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.

The FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation for VY-AADC for the treatment of Parkinson's disease in patients with motor fluctuations that are refractory to medical management. RMAT designation is an expedited program for the advancement and approval of regenerative medicine products, including gene therapy products. RMAT designation was granted based on clinical data from the Phase 1b trial with VY-AADC in patients with Parkinson's disease. During this trial, one-time administrations of VY-AADC demonstrated robust and durable improvements in patients' motor function along with substantial reductions in use of daily oral levodopa and other Parkinson's disease medications. Infusions of VY-AADC have been well-tolerated in this trial with no vector-related serious adverse events reported to date.

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. 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,” “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, 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.

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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