VistaGen and NIH Sign Agreement for NIH-Sponsored Phase 2 Study of Orally-Active AV-101 in Major Depressive Disorder

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Similar to Ketamine, AV-101 Has a Fundamentally Novel Mechanism of Action Compared to All Approved Antidepressants

SOUTH SAN FRANCISCO, CA -- (Marketwired) -- 02/17/15 -- VistaGen Therapeutics, Inc. (OTCQB: VSTA), a clinical-stage biopharmaceutical company developing innovative medicine for depression and conditions involving the central nervous system (CNS), has entered into a Cooperative Research and Development Agreement (CRADA) with the U.S. National Institute of Mental Health (NIMH), part of the U.S. National Institutes of Health (NIH). Under the CRADA, VistaGen and the NIMH will collaborate on an NIH-sponsored Phase 2 clinical study of AV-101, VistaGen's orally-active NMDA receptor modulator, in subjects with Major Depressive Disorder (MDD). MDD is a widespread and debilitating mental disorder affecting millions worldwide, including nearly 7% of U.S. adults.

Dr. Carlos Zarate, Chief of the Section on the Neurobiology and Treatment of Mood Disorders and Chief of the Experimental Therapeutics and Pathophysiology Branch at the NIMH, will be the Principal Investigator of the NIH-funded study, which will be a randomized, double-blind, placebo-controlled, crossover Phase 2 clinical trial designed to evaluate the efficacy and safety of a single oral dose of AV-101 administered once per day for 14 days to approximately 25 subjects with MDD. The primary efficacy measure will be the Hamilton Depression Rating Scale (HDRS), a standard scale for measuring depression severity. VistaGen and the NIH anticipate completing the study in 2015.

"We are excited by the strong preclinical efficacy data supporting the ketamine-like antidepressant effects of AV-101, as well as the rapid and efficient oral-delivery and clinical safety range demonstrated by our successful Phase 1 clinical studies," said H. Ralph Snodgrass, VistaGen's President and CSO. "Dr. Zarate and his team have deep experience with ketamine and other NMDA receptor antagonists. We look forward to collaborating closely with them to complete this important AV-101 Phase 2 study in MDD by year end."

About MDD and Current Antidepressants
Most people will experience depressed mood at some point during their lifetime, but MDD is different. MDD is the chronic, pervasive feeling of utter unhappiness and suffering, which impairs daily functioning. Symptoms of MDD include diminished pleasure in activities, weight changes, insomnia or hypersomnia, psychomotor agitation, fatigue, feelings of worthlessness and guilt, poor concentration and suicidal thoughts and behaviors. Suicide is estimated to be the cause of death in up to 15% of individuals with MDD.

Current medications available in the multi-billion dollar global antidepressant market, including selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have limited effectiveness, and because of their mechanism of action, SSRIs and SNRIs must be taken for several weeks before patients experience any significant therapeutic benefit. Over 60% of depression sufferers do not benefit from first round treatments, and the likelihood of achieving remission of depressive symptoms declines with each successive treatment attempt. Although approximately two out of three patients may find an antidepressant drug or drug combination that induces remission of their depressive symptoms after as many as four treatment attempts during the course of up to more than a year, this trial and error process and the systemic effects of the various antidepressant medications involved increases the risks of patient tolerability issues and serious side effects, including suicidal thoughts and behaviors.

About Ketamine for MDD
In randomized, placebo-controlled, double-blind clinical trials conducted by Dr. Zarate and others at the NIMH, ketamine (an NMDA receptor antagonist which acts as an NMDA channel blocker) produced robust and rapid, within hours, antidepressant effects in MDD patients who had not responded to approved antidepressants. Although the potential for widespread therapeutic use of ketamine is limited by its potential for abuse, dissociative and psychosis-like side effects, and practical challenges associated with its required intravenous administration in a medical center, the discovery of ketamine's rapid onset antidepressant effects revolutionized thinking about the MDD treatment paradigm and mechanism of action of antidepressant medicines. The discovery also increased interest in the development of a new generation of antidepressants with a mechanism of action similar to ketamine's, including a more rapid therapeutic benefit compared to existing agents.

About AV-101 for MDD
AV-101 is a unique, orally-active, prodrug candidate that produces, in the brain, 7-chlorokynurenic acid (7-Cl-KYNA), one of the most potent and selective antagonists of the glycine-binding site of the NMDA receptor, resulting in the down-regulation of NMDA signaling. Growing evidence suggests that the glutamatergic system is central to the neurobiology and treatment of MDD and other mood disorders.

AV-101's fundamentally novel mechanism of action places it among a new generation of glutamatergic antidepressants with breakthrough potential to treat millions of MDD sufferers worldwide who are poorly served by SSRIs, SNRIs and other current depression therapies. Like ketamine, AV-101 modulates (down-regulates) NMDA receptor channel activity. However, unlike ketamine's antagonistic activity, which results from its blocking the NMDA receptor channel, AV-101's antagonistic activity results from its selective binding to, and blocking of, the functionally-required glycine-binding co-agonist site of the NMDA receptor. Targeting the glycine-binding co-agonist site of the NMDA receptor may bypass potential adverse effects that occur with ketamine without affecting the robust efficacy observed in previous clinical studies. This may then result in the "glutamate surge" that has been associated with the rapid-acting antidepressant effects of ketamine.

The NIH previously awarded VistaGen $8.8 million to advance its preclinical and Phase 1 clinical development of AV-101. In two randomized, double-blind, placebo-controlled Phase 1 safety studies, AV-101 was well tolerated and not associated with any severe adverse events. There were no signs of sedation, hallucinations or schizophrenia-like side effects often associated with ketamine and traditional NMDA receptor channel blockers.

About the U.S. National Institute of Mental Health
The U.S. National Institute of Mental Health (NIMH), part of the U.S. National Institutes of Health (NIH), is the largest scientific organization in the world dedicated to mental health research. NIMH is one of 27 Institutes and Centers of the NIH, the world's leading biomedical research organization. The mission of NIMH is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery and cure. For more information, visit www.nimh.nih.gov.

About VistaGen Therapeutics
VistaGen is a clinical-stage biopharmaceutical company developing innovative medicine for depression and diseases and conditions involving the central nervous system (CNS). VistaGen's AV-101 is a new generation orally-available NMDA receptor glycine B-site antagonist entering Phase 2 clinical development for Major Depressive Disorder. Based on preclinical studies, AV-101 may also have potential as a treatment for other CNS-related conditions, including chronic neuropathic pain and epilepsy, as well as neurodegenerative diseases such as Parkinson's disease and Huntington's disease. VistaGen is also leveraging its proprietary pluripotent stem cell technology and clinically-predictive bioassay systems, CardioSafe 3D™ and LiverSafe 3D™, for drug rescue applications focused on producing proprietary new chemical entities (NCEs) that are novel, safer versions of drug candidates previously optimized and tested for efficacy by pharmaceutical companies and others but terminated before FDA approval due to heart or liver toxicity.

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Cautionary Statement Regarding Forward-Looking Statements
The statements in this press release that are not historical facts may constitute forward-looking statements that are based on current expectations and are subject to risks and uncertainties that could cause actual future results to differ materially from those expressed or implied by such statements. Those risks and uncertainties include, but are not limited to, risks related to the VistaGen's and the NIH's successful completion of the NIH-sponsored Phase 2 clinical study of AV-101 in MDD under the CRADA, its stem cell technology-based drug rescue activities, protection of its intellectual property, and the availability of substantial additional capital to support its operations, including the foregoing activities. These and other risks and uncertainties are identified and described in more detail in VistaGen's filings with the Securities and Exchange Commission (SEC). These filings are available on the SEC's website at www.sec.gov. VistaGen undertakes no obligation to publicly update or revise any forward-looking statements.

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