



## VistaGen Receives FDA and NIH Clearance to Initiate NIH-Funded Phase 2 Study of Orally Active AV-101 in Major Depressive Disorder

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### Phase 2 Clinical Study in Major Depressive Disorder Expected to Commence at NIH in 3Q 2015

SOUTH SAN FRANCISCO, CA -- (Marketwired) -- 07/01/15 -- VistaGen Therapeutics, Inc. (OTCQB: VSTA), a clinical-stage biopharmaceutical company committed to developing and commercializing innovative product candidates for patients with depression, other diseases and various disorders related to the central nervous system as well as cancer, has received clearance from the U.S. Food and Drug Administration (FDA) and the U.S. National Institutes of Health (NIH) to initiate an NIH-funded Phase 2 clinical study of its orally active AV-101 in subjects with treatment-resistant Major Depressive Disorder (MDD) under protocol number 15-M-0151. The Principal Investigator of the study will be Dr. Carlos Zarate, Jr., Chief of the Section on the Neurobiology and Treatment of Mood Disorders and Chief of the Experimental Therapeutics and Pathophysiology Branch at the U.S. National Institute of Mental Health (NIMH), which is part of the NIH. The Phase 2 study will be a randomized, double-blind, placebo-controlled, crossover clinical trial conducted at the NIMH and 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 patients with MDD. VistaGen and the NIMH expect to initiate enrollment of subjects in the study in 3Q 2015.

AV-101 is an orally active, clinical-stage prodrug candidate that readily gains access to the central nervous system (CNS) after systemic administration and is rapidly converted *in vivo* to its active metabolite, 7-chlorokynurenic acid (7-Cl-KYNA), a well-characterized, potent, and highly-selective antagonist of the glycine-binding co-agonist (GlyB) site of the N-methyl-D-aspartate receptor (NMDAR). Current evidence suggests that AV-101's antagonism of NMDAR signaling may provide fast-acting antidepressant effects in the treatment of MDD. In addition, as confirmed in two Phase 1 clinical studies, using AV-101 to target the GlyB site of the NMDAR may bypass potential adverse effects that occur with ketamine, while activating similar pathways resulting in the "glutamate surge" that has been associated with increased neurogenesis and the rapid-acting antidepressant effects of ketamine observed in previous clinical studies.

"The NIMH and several key leaders in the field with clinical experience using ketamine to treat MDD provided valuable expert advice on the design of our Phase 2 MDD study. We are grateful for their assistance. With their help, we have now achieved an important regulatory milestone for our AV-101 clinical development program," said H. Ralph Snodgrass, the Company's President and Chief Scientific Officer. "The pharmacology and existing clinical safety data and preclinical efficacy data point to AV-101's potential to provide a transformative advancement in the treatment of MDD, in a manner fundamentally different from all currently approved antidepressants."

#### *About MDD*

While most people will experience episodic depressed mood at multiple points during their life, MDD is different. MDD is the chronic, pervasive feeling of utter unhappiness, hopelessness and suffering, which impairs daily functioning. Symptoms of MDD include diminished pleasure in activities, changes in appetite that result in weight changes, insomnia or oversleeping, psychomotor agitation, loss of energy or increased fatigue, feelings of worthlessness or inappropriate guilt, difficulty thinking, concentrating or making decisions, and thoughts of death and attempts at suicide. Suicide is estimated to be the cause of death in up to 15% of individuals with MDD. MDD is one of the most common mental disorders in the United States. According to the NIMH, about 6.7% of U.S. adults experience MDD each year.

#### *About Current Antidepressants*

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. Because of their mechanism of action, SSRIs and SNRIs must be taken for several weeks before patients experience significant therapeutic benefit. Approximately two-thirds of depression sufferers do not benefit from initial treatment with SSRIs and SNRIs. Although approximately two-thirds patients may find an antidepressant drug or drug combination that induces remission of their depressive symptoms after several different drug treatment attempts, 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 the potential of increased suicidal thoughts and behaviors during the time period before the therapeutic effects of the drugs are obtained.

#### *About Ketamine for MDD*

Ketamine hydrochloride (ketamine) is an FDA-approved, rapid-acting general anesthetic. The use of ketamine to treat MDD has been studied in several clinical trials conducted by depression experts, including Dr. Carlos Zarate and others at the NIMH. In randomized, placebo-controlled, double-blind clinical trials reported by Dr. Zarate and others at the NIMH, a single subanaesthetic intravenous dose of ketamine (0.5 mg/kg over 40 minutes) produced robust and rapid antidepressant effects in MDD patients who had not responded to currently-approved medications. These results were in contrast to the slow onset of currently FDA-approved antidepressant medications, which usually require many weeks or months of chronic usage to achieve similar antidepressant effects. The potential for widespread therapeutic use of ketamine is severely limited by its potential for abuse, dissociative and psychosis-like side effects, and by practical challenges associated with its intravenous administration in a medical center. Notwithstanding these limitations the discovery of ketamine's fast-acting antidepressant effects revolutionized thinking about the MDD treatment paradigm. The discovery also increased interest in the development of a new generation of antidepressants with a fast-acting mechanism of action similar to ketamine's.

#### *About AV-101 for MDD*

AV-101's fundamentally novel mechanism of action places it among a new generation of glutamatergic antidepressants with 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) NMDAR activity. However, unlike ketamine's antagonistic activity, which results from its blocking the NMDAR ion channel, AV-101's antagonistic activity results from its selective binding to, and blocking of, the functionally-required GlyB site of the NMDAR. In addition, AV-101 is orally available and has a much longer half-life than ketamine and mechanistically similar peptides currently under development for MDD.

#### *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](http://www.nimh.nih.gov).

#### *About VistaGen Therapeutics*

VistaGen Therapeutics, Inc. is a clinical-stage biopharmaceutical company committed to developing and commercializing innovative product candidates for patients with depression, other diseases and various disorders related to the central nervous system as well as cancer. VistaGen's AV-101 is a new generation orally-available NMDAR GlyB antagonist in 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 developing and using 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) for its internal development pipeline.

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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, 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](http://www.sec.gov). VistaGen undertakes no obligation to publicly update or revise any forward-looking statements.

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