Favorable Data on VistaGen Therapeutics' AV-101 for Major Depressive Disorder Published in Peer-reviewed Journal of Pharmacology and Experimental Therapeutics

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Pre-clinical Study Results Show Equal Efficacy and Improved Safety Profile Compared with Ketamine

SOUTH SAN FRANCISCO, Calif., Sept. 16, 2015 /PRNewswire/ -- VistaGen Therapeutics, Inc. (OTCQB: VSTA), a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat depression, cancer and diseases and disorders involving the central nervous system (CNS), today announced that pre-clinical data on its lead pipeline candidate, AV-101 – an orally-available new generation prodrug candidate for Major Depressive Disorder (MDD) and other CNS related indications – will be published in the October 2015 issue of the peer-reviewed, *Journal of Pharmacology and Experimental Therapeutics.* The article, entitled, *The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition,* is authored by Zanos, et al., and is currently available online at http://jpet.aspetjournals.org/content/early/2015/08/11/jpet.115.225664.abstract.

Data from the published study, which utilized four, widely accepted animal models for evaluating antidepressive drugs, showed rapid, dose-dependent and persistent ketamine-like antidepressant effects following a single treatment. Moreover, AV-101 administration was not associated with negative side effects usually attributed to ketamine, such as addictive preference, psychotomimetic responses, and abnormal locomotor or movement behaviors. As a result, these study results provide additional support for VistaGen's contention that antagonism of the regulatory co-agonist glycine-binding (GlyB) site of the N-methyl-D-aspartate receptor (NMDAR) in the brain constitutes a promising new approach for the treatment of patients suffering from MDD. Management believes that the efficacy of the Company's approach may be further enhanced by the fact that AV-101's active metabolite (7-chlorokynurenic acid) – the active form of the drug after it has been processed by the body -- is 20-times more active and selective than the naturally occurring kynurenic acid, an important neurotransmitter, which is produced by astrocytes. The prodrug mechanism of AV-101 supports critical functions of astrocyte (the most numerous non-neuronal brain cells), by delivering a significantly more potent and selective chemical variant of KYNA, a key regulator of NMDAR that is normally produced by astrocytes in the brain. This is important because astrocyte function is very often impaired in individuals with MDD, and suicidal patients have been shown to have abnormally low levels of KYNA in the brain. Furthermore, astrocytes are critical for normal neuronal function because they also regulate glucose metabolism, neurotransmitter uptake (particularly for glutamate) and synaptic development.

As announced in July 2015, VistaGen 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 AV-101 in subjects with treatment-resistant MDD. Enrollment in this study is expected to commence this month. The Phase 2 study will be a randomized, double-blind, placebo-controlled, crossover clinical trial conducted at the U.S. National Institutes of Mental Health (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 treatment-resistant MDD. The Principal Investigator of this study is Dr. Carlos Zarate, Jr., Chief of Experimental Medicine at the NIMH.

"Today, there is a major need for new treatment options for patients with MDD, due to frequent resistance and significant delays in providing therapeutic benefit associated with currently approved treatments," stated H. Ralph Snodgrass, President and Chief Scientific Officer of VistaGen. "AV-101's emerging efficacy and safety profile suggest a clear potential to provide fast-acting and long-duration antidepressant effects while bypassing the adverse reactions associated with ketamine treatment – and which therefore limit ketamine's potential usefulness. AV-101's oral administration is also a key differentiating factor compared to today's other development-stage products which are given intravenously."

Commenting on today's news, Dr. Gerard Sanacora, Director of the Yale Depression Research Program, and member of VistaGen's Clinical and Scientific Advisory Board, noted, "The discovery of ketamine's fast-acting antidepressant effects has catalyzed the development of a new generation of novel drug candidates that hold the promise to fundamentally change the approach to treating acute depressive episodes. The recent findings showing AV-101 to have antidepressant-like effects similar to ketamine in several rodent models, and demonstrating evidence that both drugs produce the effects through similar mechanisms of action, suggest that AV-101 acts through similar pathways as ketamine. However, the lack of significant effects on models examining psychotomimetic-like behaviors and locomotor disruption with AV-101 suggest the possibly that unique, dissociable, mechanisms are involved in generating the antidepressant actions and the unwanted side effect profile that are commonly seen with ketamine administration. If this is in fact the case, it is quite possible that AV-101 could provide patients with similar, rapid and sustained antidepressant benefits without the unwanted side effects associated with ketamine."

About MDD

While most people will experience episodic depressed moods 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. MDD is one of the most common mental disorders in the United States and is a leading cause of disability. According to the NIMH, MDD affects nearly 7% of the U.S. adult population 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), are ineffective for millions of patients who battle MDD every day. According to Rush, A. J., et al.

(2006) "Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report." *Am J Psychiatry* **163**:1905-1917, approximately two-thirds of depression sufferers do not benefit from initial treatment with SSRIs and SNRIs. Due to their mechanism of action, SSRIs and SNRIs must be taken for several weeks before those patients who do respond, can expect to experience significant therapeutic benefit. Although approximately two-thirds of patients may eventually find an antidepressant drug or drug combination that reduces 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 a subanesthetic-dose of ketamine to treat MDD has been studied in several clinical trials conducted by depression experts, including Dr. Carlos Zarate, Jr. and others at equally well-known clinical research institutions. In randomized, placebo-controlled, double-blind clinical trials reported by Dr. Zarate and his colleagues at the NIMH, a single subanesthetic intravenous dose of ketamine (0.5 mg/kg over 40 minutes) produced a robust, up to 70% response rate, and rapid antidepressant effects in MDD patients who had not previously responded to currently-approved medications. These results were in contrast to the slow onset of action generated by currently FDA-approved antidepressant medications, which, if effective for a specific individual, 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 has revolutionized thinking about the MDD treatment paradigm.

About AV-101 for MDD

AV-101's fundamentally novel mechanism of action places it among a new generation of glutamatergic antidepressants with the 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 it directly blocking the NMDAR ion channel, AV-101's antagonistic activity results from its selective binding to the functionally-required GlyB site, resulting in a concentration-dependent downregulation of the NMDAR. AV-101 is orally formulated with efficient and rapid delivery of the prodrug as well as the active metabolite to the blood and the brain, with a much longer half-life than ketamine and peptides currently under development for MDD, which target the NMDAR GlyB site. In addition, two clinical trials have shown AV-101 to be very safe and well-tolerated, and even at the highest dose studied AV-101 had a safety profile similar to that seen with the placebo control.

About VistaGen Therapeutics

VistaGen Therapeutics, Inc. is a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat depression, cancer and diseases and disorders involving the central nervous system (CNS). 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 using pluripotent stem cell technology for potential commercial applications focused on producing proprietary new chemical entities (NCEs) through drug rescue and regenerative therapies related to diseases and conditions related to blood, cartilage, heart and liver cells. For additional information, please visit www.VistaGen.com.

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. VistaGen undertakes no obligation to publicly update or revise any forward-looking statements.

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