VistaGen's PH10 Nasal Spray Demonstrates Different Mechanism of Action from Benzodiazepines in Preclinical Study

March 11, 2021

PH10 may have stand-alone potential to displace current oral antidepressants in the drug treatment paradigm for depression disorders

SOUTH SAN FRANCISCO, Calif., March 11, 2021 (GLOBE NEWSWIRE) -- VistaGen Therapeutics, Inc. (NASDAQ: VTGN), a biopharmaceutical company committed to developing and commercializing a new generation of medicines with the potential to go beyond the current standard of care for anxiety, depression and other central nervous system (CNS) disorders, today announced preclinical data demonstrating that the potential mechanism of action of PH10, its Phase 2 investigational pherine nasal spray with potential as a rapid-onset, stand-alone treatment for major depressive disorder (MDD), does not involve direct activation of GABA-A receptors, in distinct contrast to the mechanism of action of benzodiazepines, which act as direct positive modulators of GABA-A receptors. Instead, PH10 is designed to engage receptors in nasal chemosensory neurons which in turn regulate neurons in the limbic amygdala that release excitatory neurotransmitters producing rapid-onset antidepressant effects.

"These preclinical data suggest that PH10's mechanism of action does not work through GABA-A receptors, unlike many other neurosteroids, suggesting it may not have benzodiazepine-like side effects, such as sedation and cognitive impairment, or abuse liability," stated Mark Smith, MD, PhD, Chief Medical Officer of VistaGen. "Using *in vitro* patch clamp electrophysiology, PH10 had no agonist or antagonist effects on GABA receptors. While PH10 may regulate endogenous GABA circuits in the brain, it does not appear to directly bind to or modulate GABA receptors at concentrations of less than 10 micromolar, which differentiates its mechanism of action from that of benzodiazepines."

In September 2020, the U.S. Food and Drug Administration (FDA) released a Drug Safety Communication (DSC) detailing the risks associated with use of benzodiazepines. According to the FDA's communication, 92 million benzodiazepine prescriptions were filled in 2019. The DSC detailed safety concerns regarding the serious risks of abuse, addiction, physical dependence, and withdrawal reactions linked to long-term use of benzodiazepines, and the FDA announced that it is requiring an updated Boxed Warning, the FDA's most prominent type of safety warning, for all benzodiazepine medications.

According to the World Health Organization, MDD affects more than 264 million adults globally. In the U.S., MDD is one of the most common mental health disorders, with over 17 million adults having experienced at least one major depressive episode within the most recent year (2017) reported by the U.S. National Institute of Mental Health. For some individuals, MDD can result in severe impairments that interfere with or limit one's ability to carry out major life activities and can have significant emotional, functional, and economic impact on those who suffer from the disorder as well as their loved ones.

The current most commonly prescribed oral antidepressants are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). SSRIs are intended to increase the amount of available serotonin by inhibiting the reuptake of serotonin in the brain, preventing nerve cells from reabsorbing serotonin and reducing the levels in the brain. SNRIs similarly are intended to inhibit the reuptake of serotonin and another neurotransmitter, norepinephrine, and increase the available amounts of each in the brain. While these medications can certainly be effective in the right context, they are associated with slow onset of action, numerous side effects and limited therapeutic benefits, often challenging for medical professionals to identify the right drug or combination of drugs for particular individuals.

Recent studies have shown that there has been an exacerbation of existing depression symptoms, with U.S. adults showing three times as many symptoms of depression during the COVID-19 pandemic, creating a critical need for new and differentiated alternatives for treatment of MDD. PH10 may have the potential to displace existing SSRIs and SNRIs as a stand-alone alternative in the drug treatment paradigm for depression disorders.

PH10 is a new generation antidepressant with a mechanism of action that is designed to be fundamentally different from all current FDA-approved antidepressants. After intranasal administration, a non-systemic microgram-level dose of PH10 binds to nasal chemosensory receptors that, in turn, activate key neural circuits in the brain that can lead to rapid-onset antidepressant effects, but without the psychological side effects or safety concerns that may be caused by rapid-onset ketamine-based therapy, including both intravenous ketamine and esketamine nasal spray, or the side effects and safety concerns of current oral antidepressants that may take many weeks to become effective.

About PH10
PH10 is a Phase 2 investigational pherine nasal spray designed to have rapid-onset effects and therapeutic potential in several neuropsychiatric indications involving depression. Self-administered in microgram-level doses, PH10 does not require systemic uptake and distribution to produce rapid-onset antidepressant effects. Following completion of a successful exploratory Phase 2A clinical study, VistaGen is preparing for a planned PH10 for a Phase 2B clinical study in the U.S. as a stand-alone treatment of MDD. With its rapid-onset pharmacology, lack of systemic exposure at clinical doses administered to-date and favorable safety results observed in all clinical studies to date, VistaGen believes PH10 has potential to be a new stand-alone treatment for several depression disorders.

About VistaGen
VistaGen Therapeutics is a biopharmaceutical company committed to developing and commercializing innovative medicines with the potential to go beyond the current standard of care for anxiety, depression, and other CNS disorders. Each of VistaGen's three drug candidates has a differentiated potential mechanism of action, has been well-tolerated in all clinical studies to date and has therapeutic potential in multiple CNS markets. For more information, please visit www.vistagen.com and connect with VistaGen on Twitter, LinkedIn, and Facebook.

Forward Looking Statements
Various statements in this release are "forward-looking statements" concerning our future expectations, plans and prospects, including the potential for successful clinical development and commercialization of PH10 for depression disorders, including MDD. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risks that: development and approval of PH10 may not be achieved in any market; the FDA or counterpart foreign regulatory authorities may decide that the results of the our PH10 clinical program are not sufficient for regulatory approval for treatment of MDD or any other depression-related disorder; development of PH10 may not be successful in any indication; success in nonclinical studies or in earlier-stage clinical trials may not be repeated or observed in future studies, which may not support further development or be sufficient to gain regulatory approval to market PH10; adverse events may be encountered at any stage of development that negatively impact further development. Other risks and uncertainties include, but are not limited to, issues related to: adverse healthcare reforms and changes of laws and regulations; general industry and market conditions; manufacturing and marketing risks, including risks related to the COVID-19 pandemic, which may include, but are not limited to, unavailability of or delays in delivery of raw materials for manufacture of PH10; inadequate and/or untimely supply of PH10 to meet demand; entry of competitive products; and other technical and unexpected hurdles in the development, manufacture and commercialization of PH10, as well as those risks more fully discussed in the section entitled "Risk Factors" in our most recent Annual Report on Form 10-K for the year ended March 31, 2020, and in our most recent Quarterly Report on Form 10-Q for the quarter and nine months ended December 31, 2020, as well as discussions of potential risks, uncertainties and other important factors in our other filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent our views only as of today and should not be relied upon as representing our views as of any subsequent date. We explicitly disclaim any obligation to update any forward-looking statements.

VistaGen Company Contact
Mark McPartland
VistaGen Therapeutics
Phone: (650) 577-3606
Email: IR@vistagen.com

VistaGen® Therapeutics

Source: VistaGen Therapeutics, Inc.

Released March 11, 2021