Vistagen Reports New Preclinical Data Supporting Itruvone (PH10) Nasal Spray's Potential Antidepressant Activity via Peripheral Nasal Neurons without Entry into the Brain

July 17, 2023

Preclinical study of radiolabeled intranasal itruvone in laboratory rats further validates itruvone's potential to treat major depressive disorder (MDD) without systemic absorption

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Jul. 17, 2023-- Vistagen (NASDAQ: VTGN) a late clinical-stage biopharmaceutical company aiming to transform the treatment landscape for individuals living with anxiety, depression and other central nervous system (CNS) disorders, today announced new mechanism of action data from a preclinical tissue distribution study in laboratory rats. The study demonstrated that a single intranasal administration of radiolabeled itruvone ([^{14}C]PH10) was essentially undetectable in the brain and most other tissues, including blood and plasma.

These new data further support the proposed mechanism of action of itruvone nasal spray as involving binding to receptors of peripheral chemosensory neurons in the nasal cavity, but not to neuronal receptors in the CNS, and thereby limiting transport of molecules to the circulatory system and minimizing potential systemic exposure.

"Itruvone's unique mechanism of action is further demonstrated in this new carbon-labeled study," said Shawn Singh, Chief Executive Officer of Vistagen. "These new data and previously announced preclinical electrophysiology data demonstrating that itruvone's mechanism of action does not involve direct activation of GABA-A receptors in the brain, as well as other completed Phase 1 and Phase 2A clinical studies, provide a substantial body of evidence supporting itruvone's exceptionally favorable safety profile. Currently approved medications to treat depression require systemic absorption. This can lead to unwanted side effects and create potential drug-drug interaction concerns for some individuals who require additional medications for other medical conditions. As a potential non-systemic treatment option, we believe itruvone has a vital opportunity to change the treatment paradigm for the growing numbers of individuals suffering from depression disorders across the globe."

Vistagen recently reported that itruvone is now staged for potential Phase 2B clinical development in the U.S. as a stand-alone treatment for MDD, building on previously published results from a randomized, double-blind, placebo-controlled Phase 2A study of itruvone in MDD. In that study, itruvone was administered intranasally at a daily dose of 3.2 µg and 6.4 µg for 8 weeks. After one week of treatment, the mean reduction on the 17-item Hamilton Depression Scale (HAM-D-17) scores for the itruvone 6.4 µg group was 10.1 points, which was statistically greater ($p = 0.03$) than the mean reduction in the placebo group of 4.2 points from baseline. Also, at the end of the last week of treatment (Week 8) in that study, the itruvone 6.4 µg group showed a mean HAM-D-17 score reduction of 17.8, which was statistically greater than the mean reduction in the placebo group of 10.9 points from baseline ($p = 0.02$). Thus, in the itruvone 6.4 µg treatment group, the HAM-D-17 score improved significantly from the baseline within one week and this effect was sustained until the Week 8 study endpoint. Notably, both the itruvone 3.2 µg and 6.4 µg treatment groups showed strong effect sizes after one week of treatment (0.72 for the 3.2 µg dose and 1.01 for the 6.4 µg dose) and at the Week 8 study endpoint (0.74 for the 3.2 µg dose and 0.95 for the 6.4 µg dose). There were no reports of SAEs. Itruvone was well-tolerated and did not cause psychological side effects (such as dissociation or hallucinations) or other safety concerns that may be associated with other approved pharmacological therapies for MDD.

About Itruvone (PH10)

Itruvone (PH10) is an investigational pherine nasal spray designed with a potential mechanism of action (MOA) that is fundamentally differentiated from the MOA of all currently approved treatments for depression disorders. Itruvone is administered at microgram-level doses and is designed to engage and activate chemosensory neurons in the nasal cavity connected to neural circuits in the brain that produce antidepressant effects. Specifically, itruvone's proposed MOA involves binding to receptors of chemosensory neurons in the nasal cavity that regulate the olfactory-amygdala neural circuits believed to increase the activity of the limbic-hypothalamic sympathetic nervous system and increase the release of catecholamines. Importantly, unlike all currently approved oral antidepressants and ketamine-based therapy (KBT), including both intravenous ketamine and intranasal ketamine, we believe itruvone does not require systemic absorption or brain penetration to produce antidepressant effects, while avoiding side effects and safety concerns potentially associated with KBT and longer acting oral antidepressants. The FDA has granted Fast Track designation for the development of itruvone as a potential treatment for major depressive disorder.

About Vistagen

Vistagen (Nasdaq: VTGN) is a late clinical-stage biopharmaceutical company aiming to transform the treatment landscape for individuals living with anxiety, depression and other CNS disorders. Vistagen is advancing therapeutics with the potential to be faster-acting, and with fewer side effects and safety concerns, than those currently available for the treatment of anxiety, depression and multiple CNS disorders. Vistagen's pipeline includes six clinical-stage product candidates, including fasedienol (PH94B), itruvone (PH10), PH15, PH80, and PH284, each an investigational agent belonging to a new class of drugs known as pherines, as well as AV-101, which is an oral prodrug antagonist of the N-methyl-D-aspartate receptor (NMDAR). Pherines are administered as low microgram dose level nasal sprays and are designed with a novel mechanism of action that activates chemosensory neurons in the nasal cavity and can beneficially impact key neural circuits in the brain without systemic uptake or direct activity on CNS neurons in the brain. Vistagen is passionate about transforming mental health care and redefining what is possible in the treatment of anxiety, depression and several other CNS disorders. Connect at www.Vistagen.com.

Forward Looking Statements

This press release contains certain forward-looking statements within the meaning of the federal securities laws. These forward-looking statements

involve known and unknown risks that are difficult to predict and include all matters that are not historical facts. In some cases, you can identify forward-looking statements by the use of words such as “may,” “could,” “expect,” “project,” “outlook,” “strategy,” “intend,” “plan,” “seek,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “strive,” “goal,” “continue,” “likely,” “will,” “would” and variations of these terms and similar expressions, or the negative of these terms or similar expressions. Such forward-looking statements are necessarily based upon estimates and assumptions that, while considered reasonable by Vistagen and its management, are inherently uncertain. As with all pharmaceutical products, there are substantial risks and uncertainties in the process of development and commercialization, and actual results or developments may differ materially from those projected or implied in these forward-looking statements. Among other things, there can be no guarantee that any of Vistagen’s drug candidates, including itruvone, will successfully complete future clinical trials, receive regulatory approval or be commercially successful or that future studies will replicate results from prior non-clinical and/or clinical studies for any of Vistagen’s drug candidates. Other factors that may cause such a difference include, without limitation, risks and uncertainties relating to securing sufficient financing or third-party collaborative support to launch, conduct and complete clinical development and commercialization of itruvone or any of the Company's other product candidates; delays in launching, conducting and/or completing ongoing and/or planned clinical trials of itruvone or any of the Company’s other product candidates; fluctuating costs of materials and other resources required to conduct the Company’s ongoing and/or planned clinical and non-clinical trials; the scope of protection provided by the U.S. patents issued for any of the Company’s drug candidates will be sufficient to deter competition; market conditions; the impact of general economic, industry or political conditions in the United States or internationally; and other technical and unexpected hurdles in the development, manufacture and commercialization of the Company’s CNS drug candidates. Certain of these risks and others are more fully discussed in the section entitled "Risk Factors" in the Company’s most recent Annual Report on Form 10-K for the fiscal year ended March 31, 2023, as well as discussions of potential risks, uncertainties, and other important factors in our other filings with the U.S. Securities and Exchange Commission (SEC). The Company’s SEC filings are available on the SEC’s website at www.sec.gov. You should not place undue reliance on these forward-looking statements, which apply only as of the date of this press release and should not be relied upon as representing the Company’s views as of any subsequent date. The Company explicitly disclaims any obligation to update any forward-looking statements, other than as may be required by law. If the Company does update one or more forward-looking statements, no inference should be made that the Company will make additional updates with respect to those or other forward-looking statements.

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