FDA Provides Positive Feedback to Vistagen Regarding Use of the Liebowitz Social Anxiety Scale (LSAS) as an Endpoint in Phase 3 Development of Fasedienol (PH94B) for Treatment of Social Anxiety Disorder

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Vistagen plans to use the LSAS as the primary efficacy endpoint for a Phase 3 clinical study designed to evaluate fasedienol as a treatment for the overall control of symptoms of social anxiety disorder (SAD)

FDA provides helpful guidance on key aspects of potential NDA-enabling development plan in SAD

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Mar. 30, 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 positive feedback from its recent engagement with the U.S. Food and Drug Administration (FDA) regarding the use of the Liebowitz Social Anxiety Scale (LSAS) as the primary endpoint for future clinical studies designed to evaluate the efficacy of a treatment for the overall control of symptoms of social anxiety disorder (SAD). With FDA feedback confirming the acceptable use of the LSAS as a primary efficacy endpoint, Vistagen is positioned to finalize key components of its potential New Drug Application (NDA)-enabling development program for fasedienol for treatment of SAD. Dr. Michael R. Liebowitz, a Columbia University psychiatrist, former director and founder of the Anxiety Disorders Clinic at the New York State Psychiatric Institute and current Managing Director of The Medical Research Network LLC in New York City, is the innovator of the LSAS and is the Principal Investigator in Vistagen's new FEARLESS program, the Company's Phase 3 development program for fasedienol for treatment of SAD.

"With positive feedback from the FDA, we're focused on advancing a clinical study design with the Liebowitz Social Anxiety Scale as the primary endpoint to study the real-world effects of fasedienol over time," said Shawn Singh, Chief Executive Officer of Vistagen. "This is an important step forward, especially as SAD is becoming even more prevalent in a post-COVID world. With today's announcement, we believe Vistagen has a clear path for the continued development of fasedienol and we are more committed than ever in our mission to create safe medicines that can improve mental health."

The LSAS

Dr. Liebowitz innovated the LSAS in the mid-1980s. Three medications, two SSRIs (paroxetine and sertraline) and one SNRI (venlafaxine extended release), are currently marketed in the U.S. for the treatment of SAD on the basis of registrational trials and subsequent FDA approvals in which the LSAS was the primary efficacy endpoint. Dr. Liebowitz was among the clinical investigators involved in the registrational efficacy trials for all of these drugs, and all of such registrational trials were positive.

The LSAS consists of 24 situations that commonly induce fear, anxiety and avoidance in SAD patients. The clinical rater asks SAD patients how fearful or anxious they felt in the past week during each of the 24 situations they experienced, or to imagine how anxious they would have been in any situation(s) not actually encountered. After rating fear and anxiety in each situation, the rater then asks how often the patient actually avoided, or would have avoided, each of the situations. This built-in internal verification between a patient's subjective feeling and actual behavior makes the LSAS unique when compared to other scales. Vistagen, in collaboration with Dr. Liebowitz, has developed a robust rater training and certification program for all clinicians assigned by the investigator to administer the LSAS in a Vistagen SAD study.

Fasedienol and the LSAS

The safety profile and potential for fasedienol to achieve overall reduction in symptoms of SAD and improvement in severity of the disorder, as measured by the LSAS, have been demonstrated in a placebo-controlled Phase 2 study after two weeks of use, as well as in a large open-label study over a period of one month and beyond. The Company believes these LSAS data suggest that studies involving multiple administrations of fasedienol over time, on an as-needed basis when subjects experience real-life, socially stressful situations, most accurately demonstrate the safety and efficacy potential of fasedienol in patients with SAD and the way fasedienol would be used by SAD patients, if approved. Each SAD patient is unique, and Vistagen believes an optimal SAD treatment is one that is individualized and tailored-to-fit by patients, as-needed, to help them engage in the anxiety-provoking situations they encounter in their daily lives with less fear and anxiety.

Additional Fasedienol Program Updates

FEARLESS-1 and PALISADE-2

Positive LSAS data from a placebo-controlled Phase 2 study and exploratory data from a large Phase 3 open label study corroborate that the LSAS is the psychometric scale best suited for assessing the efficacy of fasedienol in future studies. Both studies evaluated multiple administrations of fasedienol by SAD patients in a real-world environment over time and showed clinically meaningful improvements using the LSAS scale. The clinical data, together with fasedienol's unique mechanism of action and pharmacological properties, support using the LSAS as the primary endpoint in the next potential Phase 3 study of fasedienol in SAD – FEARLESS-1. The Company also plans to include a second LSAS-based Phase 3 study and an open-label long term safety study in its potential NDA-enabling FEARLESS Phase 3 program for fasedienol in SAD. In addition to the positive FDA feedback regarding the use of the LSAS as the primary endpoint, the FDA also provided guidance on further characterizing the optimal fasedienol dosing strategy. The Company plans to have further protocol discussions with the FDA regarding additional dosing study(s), which the Company plans to conduct in parallel with FEARLESS-1 and potentially prior to commencement of the second LSAS-based Phase 3 study, to provide further foundational information about dosing frequency for purposes of labeling should fasedienol be approved.

Although the results of the interim analysis of PALISADE-2 indicated that continuation of the study would not be futile, Vistagen has determined the best course of action is to close the PALISADE-2 study given the expense, time, and methodological complexities involved in resuming PALISADE-2, including consistently administering the protocol for the single-dose, clinic-based public speaking challenge study across numerous sites. Considering the recent feedback from the FDA regarding use of the LSAS in future clinical studies, Vistagen will focus resources primarily on the planning and preparation for FEARLESS-1, a LSAS-based Phase 3 study of fasedienol for treatment of SAD. Topline results from the 140 subjects who completed PALISADE-2 are expected in the second half of 2023.

Exploratory Phase 2A Study in Adjustment Disorder with Anxiety

Adjustment disorder with anxiety (AjDA) is clinically understudied, difficult to diagnose, presents with highly variable symptoms across patients and has uncertain boundaries in patients with pre-existing psychiatric disorders. Vistagen's small exploratory study in AjDA is believed to be the first ever randomized, double-blind, placebo-controlled Phase 2A study in the U.S. aimed at exploring the pharmacological treatment of AjDA, and the first clinical trial that evaluated the effects of a fixed dosing regimen of fasedienol, involving intranasal administration of 3.2 µg of fasedienol four times per day over four weeks. A total of 71 subjects were screened for the study, 41 were randomized, 7 discontinued, and 34 completed four weeks of treatment. The study, which was not designed to achieve statistical significance, did not demonstrate a clinically significant difference between fasedienol and placebo as measured on the clinician-rated Hamilton Anxiety Scale (HAM-A). Site variances and high drug and placebo response rates were observed, likely related to the various aspects of AjDA that make it challenging to study. The study of AjDA is complicated because the disorder is by definition temporary and self-resolving, making it difficult to identify the cause of clinical improvement or whether placebo played a role in any improvement observed. AjDA is a temporary stress reaction. The stress reaction typically starts within three months of an identifiable stressful situation, but because the disorder is directly linked to a stressor, once it ends, the anxiety reaction may also end, with or without treatment.

Fixed dosing of fasedienol four times per day over four weeks was safe and well tolerated, with no appreciable differences in treatment-emergent adverse effects (TEAEs) between fasedienol and placebo. All reported TEAEs were of mild or moderate severity, with no severe or serious TEAEs reported during the study. Headache was the most commonly reported TEAE, reported by 3 subjects (15.8%) on fasedienol and 2 subjects (9.1%) on placebo.

Despite the methodological challenges inherent in the exploratory Phase 2A study in AjDA, the Company believes fasedienol builds resilience against anxiety and reduces the cognitive and physical paralysis that occurs during moments of heightened anxiety and stressful situations. Results of the AjDA study may provide support for an as-needed (PRN) fasedienol dosing approach over time as the preferred mode of treatment. Vistagen believes fasedienol modulates autonomic activity and that taking fasedienol on demand, as-needed immediately before or during anxiety-provoking situations, instead of on a fixed schedule (as in the AjDA study), may be the best way to demonstrate the anti-anxiety, or anxiolytic, effects of fasedienol and if approved, the best way for patients to use the drug in the real world for the treatment of SAD.

About Fasedienol (PH94B)

Vistagen's fasedienol (PH94B) is a first-in-class, rapid-onset investigational pherine nasal spray with a novel proposed mechanism of action (MOA) that regulates the olfactory-amygdala neural circuits of fear and anxiety and attenuates the tone of the sympathetic autonomic nervous system, without systemic distribution, potentiation of GABA-A or direct activity on CNS neurons in the brain. Vistagen is developing fasedienol in a Phase 3 program for the treatment of social anxiety disorder. Designed for intranasal administration in low microgram doses, the proposed novel MOA of fasedienol is fundamentally differentiated from all currently approved anti-anxiety medications, including all antidepressants and benzodiazepines.

About Social Anxiety Disorder

Social anxiety disorder (SAD) affects an estimated 25 million Americans. A person with SAD feels intense, persistent symptoms of anxiety or fear in certain social situations, such as meeting new people, making comments in a business meeting, dating, being on a job interview, answering a question in class, or talking to a cashier in a store. Doing common, everyday things in front of people causes profound anxiety or fear of being embarrassed, evaluated, humiliated, judged, or rejected. SAD can get in the way of going to work, attending school, or doing a wide variety of things in a situation that is likely to involve interpersonal interaction. It can lead to avoidance and opportunity costs that can significantly impact a person's employment and social activities and be very disruptive to their overall quality of life. SAD is commonly treated long-term with certain FDA-approved antidepressants, which have a slow onset of effect (several weeks) and provide limited therapeutic benefits, and benzodiazepines, which are not FDA-approved for the treatment of SAD. Both antidepressants and benzodiazepines have known side effects and significant safety concerns that may make them unattractive to individuals affected by SAD.

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. The Company is advancing therapeutics with the potential to be faster-acting, and with fewer side effects and safety concerns, than those that are currently available for treatment of anxiety and depression. Vistagen's product candidates belong to a new class of drugs known as pherines, which are designed with a novel rapid-onset mechanism of action that activates chemosensory neurons in the nasal passages 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 and depression. 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 development may differ materially from those projected or implied in these forward-looking statements. Among other things, there can be no guarantee that any of the Company's drug candidates will successfully complete ongoing or future clinical trials, receive regulatory approval or be commercially successful. Other factors that may cause such a difference include, without limitation, risks and uncertainties relating to the Company's ability to secure adequate financing for its operations,

including financing or collaborative support for continued clinical development of fasedienol (PH94B) in SAD; whether the Company's future interactions with the FDA will have productive outcomes; the completion and results of the Company's ongoing clinical studies of certain of the Company's other product candidates, itruvone (PH10) and AV-101; incorporation of PH15, PH80 and PH284 into the Company's preclinical and clinical development plans and other risks and uncertainties related to delays in launching, conducting and/or completing ongoing and planned clinical trials; the scope and enforceability of the Company's patents; fluctuating costs of materials and other resources and services required to conduct the Company's ongoing and/or planned clinical and non-clinical trials; 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. These risks 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, 2022, and in the Company's most recent Quarterly Report on Form 10-Q for the quarter ended December 31, 2022, 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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