Vistagen Receives Notice from European Patent Office of Intention to Grant Patent for AV-101 to Treat Neuropathic Pain

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Preclinical data in four well-established preclinical models of pain associated with tissue inflammation and nerve injury demonstrate AV-101's robust effects similar to gabapentin but with a better side effect profile

Phase 1 data demonstrate AV-101 is well-tolerated, with no meaningful difference in adverse events between AV-101 and placebo at any dose tested

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Dec. 27, 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 that the European Patent Office (EPO) issued a Notice of Intention to Grant a patent related to the use of AV-101 for the treatment of neuropathic pain. AV-101 is the Company's investigational oral prodrug of 7-chloro-kynurenic acid (7-Cl-KYNA), a potent and selective full antagonist (i.e., inhibitor) of the glycine coagonist site of the N-methyl-D-aspartate receptor (NMDAR). The patent, once granted, will not expire until at least 2034 and will become part of Vistagen's global patent portfolio on therapeutic uses and manufacturing techniques for AV-101.

AV-101 Preclinical Data in Pain Models

Preclinical data previously published in the peer-reviewed journal, *The Journal of Pain,*[1] demonstrate robust antinociceptive effects, similar to gabapentin, but with a better side effect profile in several preclinical models of hyperalgesia and allodynia. In the study, AV-101 prodrug was systematically administered in four rat models of pain to examine its analgesic and behavioral profile. Dose-dependent anti-hyperalgesia effects were shown in the four models of pain. Compared to the control drugs tested (gabapentin and MK-801), AV-101 has similar robust anti-nociceptive effects but, contrary to the control drugs tested, AV-101 had no discernable negative side effects. The preclinical study was conducted by Tony L. Yaksh, PhD, Professor of Anesthesiology and Pharmacology at the University of California, San Diego.

Further preclinical research conducted by Dr. Yaksh comparing AV-101 to pregabalin in the Chung ligation model of pain, an accepted gold standard preclinical model for chronic neuropathic pain caused by nerve damage, demonstrated that AV-101 had a significant dose response with similar efficacy in this rat model of a mononeuropathy as compared to pregabalin, which was used as an active comparator. The statistically significant positive preclinical results suggest AV-101's potential to treat multiple hyperpathic pain states. [2]

AV-101 Phase 1 Clinical Data

Additionally, clinical data from both the single and multi-dose Phase 1 studies previously published in the peer-reviewed publication, *Scandinavian Journal of Pain*,[3] indicated that oral AV-101 was well-tolerated, with no meaningful difference in adverse events at any dose between AV-101 and placebo. Although the AV-101 study was not designed to achieve statistical significance in reducing pain in healthy volunteers, there were consistent reductions for allodynia pain and mechanical and heat hyperalgesia. The study was conducted by Mark S. Wallace, MD, Professor of Anesthesiology and Pain Management Specialist at the University of California, San Diego.[4]

The preclinical data involving gabapentin and pregabalin, paired with the favorable safety and tolerability profile of AV-101 in all clinical studies completed to date, as well as previously reported positive preclinical results in levodopa-induced dyskinesia (LID) associated with Parkinson's therapy, demonstrate potential for Phase 2 development of AV-101 as a new non-opioid treatment alternative for multiple CNS disorders.

Vistagen plans to seek potential strategic collaborations to further advance the clinical development and commercialization of AV-101.

About AV-101

AV-101 (4-Cl-KYN) is an investigational oral prodrug of 7-chloro-kynurenic acid (7-Cl-KYNA), a potent and selective full antagonist of the glycine binding site of the NMDAR that modifies the function of the NMDAR. Unlike classic channel-blocking NMDAR antagonists such as ketamine and amantadine, 7-Cl-KYNA is not an ion channel blocker, which the Company believes is the reason for the compound's comparatively improved safety and tolerability profile. In clinical and nonclinical testing completed to date, AV-101 has demonstrated good oral bioavailability and an excellent pharmacokinetic (PK) profile. No binding of AV-101 or 7-Cl-KYNA to off-site targets was identified by an extensive receptor screening study. Moreover, in all clinical trials completed to date, AV-101 has been well-tolerated with no serious adverse psychological side effects or other safety concerns that are often observed with classic channel-blocking NMDAR antagonists. Moreover, clinical studies to date also suggest an improved side effect profile vs. other non-opioid drugs approved to treat conditions associated with pain, such as gabapentin (approved to treat post-herpetic neuralgia and adjunctively to treat partial onset epileptic seizures) and pregabalin (approved to treat neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia), both of which produce sedation in some patients.

A range of preclinical and Phase 1 clinical studies suggest AV-101's therapeutic potential in multiple CNS indications, including levodopa-induced dyskinesia, neuropathic pain, and seizures. The U.S. FDA has granted Fast Track designation for development of AV-101 as a potential non-opioid treatment for neuropathic pain. Vistagen plans to seek strategic partnering support to further advance the potential clinical development and commercialization of AV-101.

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), ituruvone (PH10), PH80, PH15, 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 of an antagonist of the N-methyl-D-aspartate receptor (NMDAR). Pherines are neuroactive nasal sprays designed with an innovative proposed mechanism of action that activates chemosensory neurons in the nasal cavity and can beneficially impact key neural circuits in the brain without systemic absorption or direct activity on 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.

[1] Yaksh, T.L., et al. (2017). "Characterization of the Effects of L-4-Chlorokynurenine on Nociception in Rodents." The Journal of Pain 18:1184-1196. https://doi.org/10.1016/j.jpain.2017.03.014

[2] Vistagen, data on file

[3] Wallace, M. et. al. (2017). "Randomized, double-blind, placebo-controlled, dose-escalation study: Investigation of the safety, pharmacokinetics, and antihyperalgesic activity of L-4-chlorokynurenine in healthy volunteers." Scandinavian Journal of Pain 17(1): 243-251. https://doi.org/10.1016/j.sjpain.2017.05.004

[4] Dr. Mark S. Wallace serves as an advisor to Vistagen

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 the scope of protection and enforceability provided by any patents issued for any of the Company's drug candidates, including AV-101, will be sufficient to deter competition, or that any of the Company's drug candidates, including AV-101, will successfully replicate past preclinical studies and/or clinical trials, 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 pursue and/or secure collaborative support for continued clinical development of AV-101; other risks and uncertainties related to delays in launching, conducting and/or completing ongoing and planned clinical trials; fluctuating costs of materials and other resources and services required to conduct the Company's ongoing and/or planned clinical and nonclinical 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 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, 2023, and in its most recent Quarterly Report on Form 10-Q for the quarter and six months ended September 30, 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. Additionally, you should not place undue reliance on these forward-looking statements in the future, because they 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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