VistaGen Therapeutics Announces Positive Preclinical Data of AV-101 Combined with Probenecid Suggesting Substantially Increased Brain Concentration Effects

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When given together with VistaGen's oral prodrug AV-101, probenecid increased brain concentrations of AV-101 7-fold and its active metabolite, 7-Cl-KYNA, 35-fold

SOUTH SAN FRANCISCO, Calif., Feb. 11, 2020 /PRNewswire/ -- VistaGen Therapeutics (NASDAQ: VTGN), a clinical-stage biopharmaceutical company developing new generation medicines for central nervous system (CNS) diseases and disorders with high unmet medical need, today announced positive preclinical data of AV-101, an oral NMDAR (N-methyl-D-aspartate receptor) antagonist prodrug, administered in combination with probenecid. The new preclinical data suggest that there is a substantially increased brain concentration of AV-101 and its active metabolite, 7-chlorokynurenic acid (7-Cl-KYNA), when given together with probenecid. These surprising effects were first revealed in the Company's recent preclinical study, although they are consistent with well-documented clinical studies of probenecid increasing the therapeutic levels of several unrelated classes of approved drugs.

"The remarkable preclinical data announced today demonstrate a 7-fold concentration increase in the brain of AV-101 prodrug, and, more importantly, a 35-fold increase of 7-Cl-KYNA, AV-101's active metabolite, when AV-101 is administered adjunctively with probenecid. We recently identified that some of the same kidney transporters that reduce drug concentrations in the blood, by excretion in the urine, are also found in the blood brain barrier and function to reduce 7-Cl-KYNA levels in the brain by pumping it out of the brain and back into the blood. In the recent studies, we discovered that blocking those transporters in the blood brain barrier with probenecid resulted in a substantially increased brain concentration of 7-Cl-KYNA," said Ralph Snodgrass, Ph.D., President and Chief Scientific Officer of VistaGen. "This 7-Cl-KYNA efflux-blocking effect of probenecid, with the resulting increased brain levels and duration of 7-Cl-KYNA, suggests the potential impact of AV-101 with probenecid could result in far more profound therapeutic benefits for patients with major depressive disorder and other NMDAR-focused CNS diseases and disorders than demonstrated in the Phase 2 studies of AV-101 in major depressive disorder completed last year," added Dr. Snodgrass.

Results on AV-101 transport with adjunctive probenecid were presented by a collaborator of VistaGen, David Dickens, Ph.D., Lecturer, Department of Molecular and Clinical Pharmacology, University of Liverpool, at the British Pharmacological Society's Pharmacology 2019 annual conference in Edinburgh, UK, in December 2019.

About Probenecid

Probenecid is a safe and well-known oral drug used to treat gout and to increase the therapeutic benefit of various antibacterial, anticancer and antiviral drugs. It is a potent inhibitor of various transporters, including the organic ion transporters in the kidney and other organs. Probenecid aids in prevention of gout by preventing the kidneys from reabsorbing uric acid from the urine, resulting in the removal of excess uric acid from the body by causing it to be excreted in urine. For certain antibacterial, antiviral and anticancer drugs, probenecid inhibits organic ion transporters in the kidney that are responsible for pumping drugs out of the blood and into the urine. Blocking these transporters results in reduced clearance and increased blood levels of drugs normally excreted by the kidneys, thus increasing their effectiveness. As recently discovered by VistaGen, some of the same kidney transporters that reduce drug concentrations in the blood, are also found in the blood brain barrier and function to reduce 7-Cl-KYNA levels in the brain

by pumping it out of the brain and back into the blood. In its recent studies, VistaGen discovered that blocking those transporters in the blood brain barrier with probenecid resulted in a substantially increased brain concentration of 7-Cl-KYNA.

About AV-101

AV-101 (4-Cl-KYN) targets the NMDAR (N-methyl-D-aspartate receptor), an ionotropic glutamate receptor in the brain. Abnormal NMDAR function is associated with numerous CNS diseases and disorders. AV-101 is an oral prodrug of 7-chloro-kynurenic acid (7-Cl-KYNA), which is a potent and selective full antagonist of the glycine co-agonist site of the NMDAR that inhibits the function of the NMDAR. Unlike ketamine and many other NMDAR antagonists, 7-Cl-KYNA is not an ion channel blocker. In all studies to date, AV-101 has exhibited no dissociative or hallucinogenic psychological side effects or safety concerns similar to those that may be caused by amantadine, esketamine and ketamine. With its exceptionally few side effects and excellent safety profile, AV-101 has potential to be an oral new generation treatment for multiple large-market CNS indications where current treatments are inadequate to meet high unmet patient needs. The FDA has granted Fast Track designation for development of AV-101 as both a potential adjunctive treatment for MDD and as a non-opioid treatment for neuropathic pain.

About VistaGen

VistaGen Therapeutics is a clinical-stage biopharmaceutical company developing new generation medicines for CNS diseases and disorders where current treatments are inadequate, resulting in high unmet need. VistaGen's pipeline is focused on clinical-stage CNS drug candidates with a differentiated mechanism of action, an exceptional safety profile in all clinical studies to date, and therapeutic potential in multiple large and growing CNS markets. For more information, please visit www.vistagen.com and connect with VistaGen on Twitter, LinkedIn and Facebook.

Forward-Looking Statements
This release contains various statements concerning VistaGen's future expectations, plans and prospects, including without limitation, our expectations regarding development and commercialization of AV-101 for various therapeutic purposes, including dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, epilepsy, major depressive disorder, neuropathic pain and suicidal ideation. In addition, statements concerning the Company's future expectations may include statements regarding intellectual property and commercial protection of each of our drug candidates. Each of these statements constitute forward-looking statements for the purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995. These forward-looking statements are neither promises nor guarantees of future performance and are subject to a variety of risks and uncertainties, many of which are beyond our control, and may cause actual results to differ materially from those contemplated in these forward-looking statements. Those risks include the following: (i) we may encounter unexpected adverse events in patients during our clinical development of any product candidate that cause us to discontinue further development; (ii) we may not be able to successfully demonstrate the safety and efficacy of our product candidates at each stage of clinical development; (iii) success in preclinical studies or in early-stage clinical studies may not be repeated or observed future studies, and ongoing or future preclinical and clinical results may not support further development of, or be sufficient to gain regulatory approval to market AV-101 or any of our product candidates; (iv) decisions or actions of regulatory agencies may negatively affect the progress of, and our ability to proceed with, further clinical studies or to obtain marketing approval for our drug candidates; (v) we may not be able to obtain or maintain adequate intellectual property protection and other forms of marketing and data exclusivity for our product candidates; (vi) we may not have access to or be able to secure substantial additional capital to support our operations, including our ongoing nonclinical and clinical development activities; and (vii) we may encounter technical and other unexpected hurdles in the manufacturing and development of any of our product candidates. Certain other risks are more fully discussed in the section entitled "Risk Factors" in our most recent annual report on Form 10-K, and subsequent quarterly reports on Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our other filings with the Securities and Exchange Commission (SEC). Our SEC filings are available on the SEC's website at www.sec.gov. In addition, any forward-looking statements represent our views only as of the issuance of this release 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.

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