VistaGen Reports Positive New Data from Second Preclinical Study of AV-101 in Combination with Probenecid

September 3, 2020

New Results Complement Earlier Positive Preclinical Data Demonstrating Increase in Brain Concentration Effects

SOUTH SAN FRANCISCO, Calif., Sept. 3, 2020 /PRNewswire/ -- VistaGen Therapeutics (NASDAQ: VTGN), a biopharmaceutical company developing new generation medicines for anxiety, depression, and other central nervous system (CNS) disorders, today announced positive new data from the Company's second preclinical study of its oral investigational drug, AV-101, in combination with probenecid. Probenecid has extensive data supporting its safe oral delivery and ability to increase the therapeutic benefit of various antibacterial, anticancer and antiviral drugs.

The results of this new study complement previous preclinical data demonstrating the combination's potential to substantially increase the brain concentration of AV-101's active metabolite, 7-Cl-KYN, a potent and selective full antagonist of the NMDA receptor glycine co-agonist site, thereby reducing, rather than blocking, NMDA receptor signaling.

"These new positive results amplify our message that AV-101, when administered in combination with probenecid, has exciting therapeutic potential across a wide range of CNS indications," said Shawn Singh, Chief Executive Officer of VistaGen. "The studies completed to date are promising and will help us determine the best next step in our overall development plan for the combination."

The second preclinical pharmacokinetic (PK) study of AV-101 and probenecid involved four groups: AV-101 (10 mg/kg and 50 mg/kg) with and without probenecid (30 mg/kg). Plasma and cerebral spinal fluid (CSF), as an indicator of brain concentration of 7-Cl-KYNA in dogs, were collected. A single oral gavage administration of AV-101 at both dose levels alone or in combination with intravenous probenecid was well-tolerated. CSF levels of both AV-101 and 7-Cl-KYNA increased roughly dose proportionally. AV-101 administered with probenecid increased the CSF 7-Cl-KYNA AUC (total drug exposure across time) by approximately 4.6 times, compared to AV-101 alone.

This PK study data are significant for three reasons: (i) CSF levels of AV-101, and especially 7-Cl-KYNA, rose dramatically, while there was only a modest increase in blood levels of AV–101; (ii) the AV–101-probenecid combination appeared safe and well-tolerated; and (iii) the significant increase in level and duration of 7-Cl-KYNA continues to suggest that adding probenecid could achieve therapeutic 7-Cl-KYNA brain levels that may not be achieved by AV-101 alone.

About VistaGen
VistaGen Therapeutics is a clinical-stage biopharmaceutical company developing new generation medicines for anxiety, depression and other CNS disorders where the current standard of care is inadequate, resulting in high unmet need. Each of VistaGen's three drug candidates has a differentiated mechanism of action, an exceptional safety profile in all studies to date, and therapeutic potential in multiple CNS markets. For more information, please visit www.vistagen.com and connect with VistaGen on Twitter, LinkedIn and Facebook.

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-chlorokynurenic 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 NMDAR antagonists that block the ion channel of the NMDAR, such as amantadine, esketamine and ketamine. With its exceptionally few side effects and excellent safety profile in all clinical studies to date, AV-101, in combination with probenecid, has potential to be an oral new generation treatment for multiple large-market CNS indications where current standard of care is inadequate.

The FDA has granted Fast Track designation for development of AV-101 as both a potential adjunctive treatment for major depressive disorder and as a non-opioid treatment for neuropathic pain.

About Probenecid
Probenecid is a safe and well-known FDA-approved oral drug used to treat gout. Probenecid is also used adjunctively to increase the therapeutic benefit of numerous 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 numerous 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 preclinical 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.

VistaGen 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 our drug candidate, AV-101, either alone or in combination with probenecid, for treatment of CNS disorders. 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 trials 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; (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 the substantial additional capital necessary to support our operations, including our ongoing and/or planned preclinical and/or clinical development studies; and (vii) we may encounter technical and other unexpected hurdles and delays 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.

View original content to download multimedia:http://www.prnewswire.com/news-releases/vistagen-reports-positive-new-data-from-second-preclinical-study-of-av-101-in-combination-with-probenecid-301123706.html

SOURCE VistaGen Therapeutics

Released September 3, 2020