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VistaGen Announces Positive Preclinical Data Supporting AV-101's Potential For Treating Levodopa-Induced Dyskinesia In Patients With Parkinson's Disease, Without The Psychological Side Effects And Safety Concerns Of Amantadine

Significant reduction of levodopa-induced dyskinesia by AV-101 observed in "gold standard" MPTP non-human primate model of Parkinson's disease, while maintaining antiparkinsonian activity of levodopa and without causing amantadine-like adverse effects

SOUTH SAN FRANCISCO, CA / ACCESSWIRE / June 20, 2019 [VistaGen Therapeutics](#) (NASDAQ: VTGN), a clinical-stage biopharmaceutical company committed to developing new generation medicines for central nervous system (CNS) diseases and disorders with high unmet need, today announced positive results of recent preclinical studies of the effects of AV-101, its oral NMDA receptor glycine site antagonist, in a widely-used MPTP non-human primate model for reproducing motor complications of Parkinson's disease (PD), including dyskinesia (sudden uncontrolled movements) observed in PD patients treated with levodopa. In the MPTP primate model, AV-101's antidyskinetic effects were similar to those generally observed with amantadine therapy, but AV-101 did not cause adverse effects experienced with amantadine.

The MPTP primate model used in this study is the "gold standard" for animal modeling of PD and has been used extensively to study both antiparkinsonian therapies and levodopa-induced dyskinesia (LID). MPTP is a neurotoxin that kills dopaminergic neurons in the striatum, producing motor symptoms similar to those of PD. In this study, AV-101's efficacy against LID was measured through behavioral scores on a dyskinesia scale, and a Parkinsonian disability scale was used to measure levodopa antiparkinsonian efficacy. This study demonstrated that AV-101 significantly ($p = 0.01$) reduced LID without affecting the timing, extent, or duration of the therapeutic benefits of levodopa. This new preclinical study was conducted by [Dr. Thérèse Di Paolo](#), Professor in the Faculty of Pharmacy at Laval University and among the world's leading researchers focused on Parkinson's disease and LID, pursuant to VistaGen's research agreement with CHU de Québec – Université Laval Research Center in Québec, Canada. Summary results of the study will be presented at an

upcoming scientific conference.

"The antidyskinetic activity of AV-101 that we measured compares favorably with our observation with amantadine in parkinsonian monkeys," said Dr. Di Paolo. "Better than amantadine, with its known side effects (in humans with Parkinson's disease and in parkinsonian monkeys), we observed no adverse effects with AV-101."

A pivotal pathological hallmark of PD is a loss of dopamine neurons in the *substantia nigra*. Loss of dopamine neurons is thought to be due to neurotoxicity associated with misfolding of proteins and is associated with increased signaling of glutamate, the most abundant excitatory neurotransmitter in the brain. Increased glutamate activity is involved with aberrant neuronal signaling and excitotoxic death of neurons.

"The NMDA receptor plays a major role in glutamatergic signaling and has been shown to be a therapeutic target for LID," said [H. Ralph Snodgrass, Ph.D.](#), VistaGen's Chief Scientific Officer. "AV-101's active metabolite, 7-Cl-KYNA, is a potent and selective NMDA receptor glycine site antagonist with neuroprotective properties. These recent results confirm our prior antidyskinesia study in this MPTP monkey model. We believe these preclinical data and AV-101's positive safety profile in all clinical studies to date support AV-101's potential to treat LID, while both maintaining the antiparkinsonian benefits of levodopa and without causing hallucinations or other serious side effects that may be associated with current amantadine-based therapy for LID," added Dr. Snodgrass.

About Parkinson's Disease

PD is the second most common neurodegenerative disease worldwide, affecting approximately one million people in the U.S. and ten million people worldwide, according to the Parkinson's Foundation. Although there is no "one-size-fits-all" description of PD, PD is a complex neurodegenerative disorder that occurs when brain cells that make dopamine, a chemical that coordinates movement, stop working or die, resulting in progressive deterioration of voluntary motor control. Classic PD motor symptoms include muscular rigidity, resting tremor, and postural and gait impairment. Typically, PD patients present with a combination of motor and non-motor symptoms. Non-motor symptoms may include cognitive impairment, sleep disorders, pain and fatigue. There is currently no medication to slow, delay, stop or cure PD, and currently available treatments are symptomatic. Treatment of motor symptoms with oral levodopa, introduced about 50 years ago, remains the gold standard treatment.

About Levodopa-Induced Dyskinesia

LID is a disorder that affects people with PD who are treated with the current standard of care, oral levodopa, for an extended period of time. Oral levodopa remains the most effective therapy for motor symptoms of PD. However, after continuous long-term use (longer than five years), many PD patients experience LID. Although clinical manifestations of LID are heterogenous, LID is commonly associated with abnormal involuntary movements, including chorea and dystonia. These motor complications tend to become more severe as PD progresses and as the duration of levodopa treatment is extended, until the impact of LID may compromise the advantage of treatment with levodopa. PD treatment with levodopa is routinely delayed due to concerns over LID. Once LID develops, levodopa-treated PD patients may be faced with a choice between immobility due to untreated and

uncontrolled PD, or mobility with the associated LID.

About AV-101

AV-101 (4-CI-KYN) belongs to a new generation of investigational medicines in neuropsychiatry and neurology known as NMDA glutamate receptor modulators. The NMDA receptor is a pivotal receptor in the brain and abnormal NMDA function is associated with multiple CNS diseases and disorders, including chronic neuropathic pain, epilepsy, major depressive disorder, LID and many others. AV-101 is an oral prodrug of 7-CI-KYNA which binds uniquely at the glycine site of the NMDA receptor and has potential to be a new at-home treatment for multiple CNS indications with high unmet need. 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 committed to developing new generation medicines for CNS diseases and disorders with high unmet need. VistaGen's [pipeline](#) includes three clinical-stage CNS drug candidates, AV-101, PH10 and PH94B. 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 our drug candidates, including AV-101 for treatment of LID in patients with PD receiving levodopa therapy, all of which 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. Among these risks is the possibility that (i) we may encounter unexpected adverse events in patients during our clinical development of any product candidate, including AV-101, that cause us to discontinue further development, (ii) we may not be able to successfully demonstrate the safety and efficacy of AV-101 or any of our other 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 in ongoing or 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 our drug candidates, including 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 substantial additional capital to support our operations, including our ongoing 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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