VistaGen Therapeutics, Inc.
Form 10-K
June 29, 2015

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

x Annual Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

For the fiscal year ended: March 31, 2015

or

¨ Transition Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Commission file number: 000-54014

VistaGen Therapeutics, Inc.
(Exact name of registrant as specified in its charter)

Nevada	20-5093315
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

343 Allerton Avenue
South San Francisco, California 94080
(650) 577-3600
(Address, including zip code, and telephone number, including area code, of registrant's principal executive office)

Securities registered pursuant to Section 12(b) of the Act

None

Securities registered pursuant to Section 12(g) of the Act

Common Stock, $0.001 par value per share

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ¨ No x

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ¨ No x

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes x

No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes S No ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. x

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ¨	Accelerated filer ¨	Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company x

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ¨ No x

The aggregate market value of the common stock of the registrant held by non-affiliates of the registrant on September 30, 2014, the last business day of the registrant's second fiscal quarter, was: $10,084,494.

As of June 25, 2015, there were 1,594,461 shares of the registrant's common stock, $0.001 par value per share, outstanding.

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Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements contained in this Annual Report on Form 10-K other than statements of historical facts, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “w
“should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about:

- the availability of capital to satisfy our working capital requirements;
- the accuracy of our estimates regarding expenses, future revenues and capital requirements;
- our plans to develop and commercialize our lead product candidate, initially as a treatment for Major Depressive Disorder;
- our ability to initiate and complete our clinical trials and to advance our product candidates into additional clinical trials, including pivotal clinical trials, and successfully complete such clinical trials;
- regulatory developments in the United States and foreign countries;
- the performance of the U.S. National Institute of Mental Health, our third-party contract manufacturer(s) and contract research organization(s);
- our ability to obtain and maintain intellectual property protection for our proprietary assets;
- the size of the potential markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates for any indication once approved;
- the success of competing products that are or become available for the indications that we are pursuing;
- the loss of key scientific or management personnel, internally from one of our third-party collaborators; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

These forward-looking statements are only predictions and we may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, so you should not place undue reliance on our

forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our business, financial condition and operating results. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Part I, Item 1A. Risk Factors, that could cause actual future results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to the Annual Report on Form 10-K with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by applicable law.

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PART I

All brand names or trademarks appearing in this report are the property of their respective holders. Unless the context requires otherwise, references in this report to "VistaGen," the "Company," "we," "us," and "our" refer to VistaGen Therapeutics, Inc., a Nevada corporation.

Item 1. Business

Company Overview

We are a clinical-stage biopharmaceutical company committed to developing and commercializing product candidates for patients with depression, other diseases and disorders related to the central nervous system (CNS), and cancer.

More than one billion people worldwide suffer from CNS disorders. Recently, the economic burden of these disorders was estimated at $2.0 trillion the United States and European Union alone, a figure that is expected to triple by 2030. The World Health Organization estimates that 350 million people are affected by depression worldwide. According to the NIH, major depression is one of the most common mental disorders in the United States. In 2012, the NIH estimated 16 million adults aged 18 or older in the U.S. had at least one major depressive episode. This represented 6.9 percent of all U.S. adults.

Our lead product candidate, AV-101, is an orally-active small molecule prodrug in Phase 2 development for Major Depressive Disorder (MDD). AV-101's mechanism of action (MOA), as an N-methyl-D-aspartate receptor (NMDAR) antagonist binding selectively at the glycine-binding (GlyB) co-agonist site of the NMDAR, is fundamentally different from all currently-approved antidepressants. In four preclinical studies utilizing well-validated animal models of depression, AV-101 was shown to induce fast-acting, dose-dependent, persistent and statistically significant antidepressant-like responses, following a single treatment, which were equivalent to responses seen with a control single sub-anesthetic dose of ketamine (sometimes used by clinicians off-label to treat suicidal behavior). In the same studies, fluoxetine (Prozac) did not induce rapid onset antidepressant-like responses. Preclinical studies also support the hypothesis that AV-101 has potential to treat several additional CNS disorders, including chronic neuropathic pain, epilepsy and neurodegenerative diseases, such as Parkinson's disease and Huntington's disease where modulation of the NMDAR may have therapeutic benefit.

Following our two successful randomized, double-blind, placebo-controlled Phase 1 safety studies funded by the U.S. National Institutes of Health (NIH), AV-101 is the only small molecule product candidate known to management that is (A) in Phase 2 clinical development as a monotherapy for MDD, (B) designed to modulate the NMDAR through antagonistic binding at the GlyB co-agonist site of the NMDAR and (C) orally-active in human subjects.

In February 2015, we entered a Cooperative Research and Development Agreement (CRADA) with the U.S. National Institute of Mental Health (NIMH), part of the NIH. Under the CRADA, we will collaborate with the NIH on a Phase 2 clinical study of AV-101 in subjects with treatment resistant MDD. Pursuant to the CRADA, the study will be conducted at the NIMH and fully-funded by the NIMH. It is contemplated that this clinical study will begin this year under the direction of Dr. Carlos Zarate, Jr., the NIMH's Chief of Experimental Therapeutics & Pathophysiology Branch and of the Section on Neurobiology and Treatment of Mood and Anxiety Disorders.

In addition to developing AV-101 for MDD and other CNS indications, we are using our stem cell technology platform for drug rescue –to identify and develop proprietary new chemical entities (NCEs) for our internal drug candidate pipeline. Drug rescue involves (1) using our customized in vitro bioassay systems to predict potential heart and liver toxicity of NCEs, (2) leveraging prior investments by pharmaceutical companies and others related to large-scale compound library screening, optimizing and testing for efficacy NCEs that were terminated before FDA

approval due to unexpected heart or liver toxicity and are now available in the public domain, and (3) applying modern medicinal chemistry to produce safer NCEs for our internal development pipeline. Our CardioSafe 3D™ bioassay system uses our human pluripotent stem cell (hPSC)-derived cardiomyocytes, or heart cells. We believe CardioSafe 3D is more comprehensive and clinically predictive than the hERG assay, which is currently the only in vitro cardiac safety assay required by FDA guidelines. Our LiverSafe 3D™ bioassay system uses our hPSC-derived hepatocytes, or liver cells, to predict potential liver toxicity of NCEs, including potential drug metabolism issues and adverse drug-drug interactions. We believe our hPSC-derived hepatocytes, which we call VSTA-heps™have more functionally useful life-span in culture than, and overcome numerous problems related to, commercially-available primary (cadaver) hepatocytes currently used in FDA-required in vitro hepatocyte assays for drug metabolism, including limited supply, unknown health status of the donor and genetic differences. CardioSafe 3D and LiverSafe 3D offer a new paradigm for evaluating and predicting potential heart and liver toxicity of NCEs, including drug rescue NCEs, early in development, long before costly, high risk animal studies and human clinical trials. We intend to develop each lead drug rescue NCE internally to establish in vitro and in vivo preclinical proof-of-concept (POC), as to both efficacy and safety, using both established in vitro and in vivo models, as well as CardioSafe 3D and, when available, LiverSafe 3D.

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Our Strategy

Our strategy is to develop, and commercialize innovative small molecule drugs that address unmet medical needs related to CNS disorders and cancer. We have assembled a management team and a team of scientific, clinical, and regulatory advisors, including recognized experts in the fields of depression and other CNS disorders, with significant industry experience to lead the development and commercialization of our product opportunities. Key elements of our strategy are to:

- Develop and commercialize our lead product candidate, AV-101, for Major Depressive Disorder (MDD). We are pursuing MDD as our lead indication for AV-101. We are preparing to launch our initial MDD Phase 2 clinical study in collaboration with the NIH in the second half of 2015. We intend to develop AV-101 internally, through Phase 3 clinical studies and submission of our NDA. If approved by the FDA, we plan to commercialize AV-101 for this indication in the U.S. either by (A) establishing or contracting for a specialty U.S. sales force focused primarily on psychiatrists and long-term care physicians who are high prescribers of currently-approved antidepressants or (B) collaborating with a pharmaceutical company with an extensive presence in U.S. CNS markets. Outside the U.S., we may choose to commercialize AV-101 in selected markets by establishing one or more strategic alliances.

- Leverage the commercial potential AV-101 by expanding to additional CNS-related disorders. We intend to pursue the development and commercialization of AV-101 in MDD and additional CNS-related indications that are underserved by currently available medicines and represent large unmet medical needs. Based on AV-101 preclinical studies, and by leveraging our AV-101 IND and successful Phase 1 clinical studies, we now have the opportunity to explore Phase 2 development of AV-101 as a potential treatment for chronic neuropathic pain, epilepsy and neurodegenerative diseases such as Parkinson’s disease and Huntington’s disease.

- Grow our internal development pipeline by pursuing drug rescue opportunities using our stem cell technology. We are using our stem cell technology to screen and develop proprietary new chemical entities (NCEs) through drug rescue programs intended to produce proprietary NCEs for our internal drug development pipeline. We will focus on NCEs with established therapeutic and commercial potential. Our ability to build on that valuable head start with our biological and electrophysiological insights regarding cardiac and liver safety effects of NCEs obtained using CardioSafe 3D and, eventually, LiverSafe 3D, we believe will help us produce and then optimize patentable drug rescue NCEs for our internal pipeline without incurring many of the substantial costs and risks typically inherent in new drug discovery and nonclinical drug development.

- Pursue other product candidates, including product candidates for treatment of CNS-related disorders. While our resources are currently focused on developing AV-101 and producing drug rescue NCEs, we may pursue additional product candidates in the future. These may be directed at CNS-related disorders and may be developed independently or in partnerships. We believe that a diversified portfolio will mitigate risks inherent in drug development and increase the likelihood of our success.

Our Product Opportunities

AV-101 (L-4-cholorkyurenine or 4-Cl-KYN)

Overview and Mechanism of Action

AV-101 is an orally-active, clinical-stage prodrug candidate that readily gains access to the central nervous system (CNS) after systemic administration and is rapidly converted in vivo to its active metabolite 7-chlorokynurenic acid (7-Cl-KYNA), a well-characterized, potent and highly selective antagonist of then N-methyl-D-aspartate receptor (NMDAR) at the glycine-binding co-agonist (GlyB) site. Prodrug pharmaceuticals are useful for their potential to

increase the selectivity of a drug for its intended target and to afford more favorable absorption, distribution, metabolism, and excretion properties.

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Current evidence suggests that AV-101's antagonism of NMDAR signaling may provide fast-acting antidepressant effects in the treatment of Major Depressive Disorder (MDD). In addition, as confirmed in our AV-101 Phase 1 clinical studies, targeting the GlyB site of the NMDAR does not have the adverse effects typically associated with classic NMDAR antagonists, such as ketamine and other NMDA channel blockers.

We believe Phase 2 clinical development of AV-101 for MDD and multiple CNS-related indications is supported by strong scientific rationale, significant IND-enabling nonclinical data, and two successful Phase 1 clinical safety studies. To date, the U.S. National Institutes of Health (NIH) has awarded us $8.8 million of grant funding for our pre-Phase 2 development of AV-101. We are currently preparing to launch our initial Phase 2 clinical trial of AV-101 in MDD.

Major Depressive Disorder

Depression is a serious medical illness and a global public health concern. The World Health Organization estimates that depression is the leading cause of disability worldwide, and is a major contributor to the global burden of disease, affecting 350 million people globally. According to the U.S. Centers for Disease Control and Prevention (CDC), approximately one in 10 Americans aged 12 and over takes antidepressant medication.

While most people will experience depressed mood at some point during their lifetime, MDD is different. MDD is the chronic, pervasive feeling of utter unhappiness and suffering, which impairs daily functioning. Symptoms of MDD include diminished pleasure in activities, changes in appetite that result in weight changes, insomnia or oversleeping, psychomotor agitation, loss of energy or increased fatigue, feelings of worthlessness or inappropriate guilt, difficulty thinking, concentrating or making decisions, and thoughts of death or suicide and attempts at suicide. Suicide is estimated to be the cause of death in up to 15% of individuals with MDD.

Current Antidepressants

For many people, depression cannot be controlled for any length of time without treatment. Current medications available in the multi-billion dollar global antidepressant market, including commonly-prescribed selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have limited effectiveness, and, because of their mechanism of action, must be taken for several weeks or months before patients experience any significant benefit. In addition, most current antidepressant medications have an FDA-required "Black Box" safety warning due to a risk of worsening depression and an increased risk of suicidal thoughts and behaviors during treatment, a property not expected to occur with AV-101. Only about 33% of depression sufferers benefit from their initial treatment, and the likelihood of achieving remission of depressive symptoms declines with each successive treatment attempt. Even after many treatment attempts during the course of up to more than a year, about 33% of depression sufferers still fail to find an effective therapy. In addition, this trial and error process and the systemic effects of the various antidepressant medications involved, increases the risks of patient tolerability issues and serious side effects, including suicidal thoughts and behaviors.

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Ketamine and NIH Clinical Studies in Major Depressive Disorder

Ketamine hydrochloride (ketamine) is an FDA-approved, rapid-acting general anesthetic. The use of ketamine (an NMDA receptor antagonist which acts as an NMDA channel blocker) to treat MDD has been studied in several clinical trials conducted by depression experts at the U.S. National Institute of Mental Health (NIMH), part of the NIH, including Dr. Carlos Zarate, Jr., the NIMH's Chief of Experimental Therapeutics & Pathophysiology Branch and of the Section on Neurobiology and Treatment of Mood and Anxiety Disorders. In randomized, placebo-controlled, double-blind clinical trials reported by Dr. Zarate and others at the NIMH, a single intravenous dose of ketamine (0.5 mg/kg over 40 minutes) produced robust and rapid antidepressant effects in MDD patients who had not responded to currently-approved medications. These results were in contrast to the slow onset of currently FDA-approved antidepressant medications, which usually require many weeks or months of chronic usage to achieve similar antidepressant effects. The potential for widespread therapeutic use of ketamine is severely limited by its potential for abuse, dissociative and psychosis-like side effects, and by practical challenges associated with its intravenous administration in a medical center. Notwithstanding these limitations, the discovery of ketamine's fast-acting antidepressant effects revolutionized thinking about the MDD treatment paradigm. The discovery also increased interest in the development of a new generation of antidepressants with a fast-acting mechanism of action similar to ketamine's. Orally-available AV-101 is among the new generation of antidepressants with potential to deliver ketamine-like antidepressant effects, without ketamine's side effects or required intravenous administration.

AV-101 and Major Depressive Disorder

AV-101 is an orally-active prodrug candidate that produces, in the brain, 7-chlorokynurenic acid (7 Cl KYNA), one of the most potent and selective antagonists of the glycine-binding site of the NMDAR, resulting in the down-regulation of NMDAR signaling. Growing evidence suggests that the glutamatergic system is central to the neurobiology and treatment of MDD and other mood disorders.

AV-101's mechanism of action is fundamentally different from currently-available antidepressants, placing it among a new generation of glutamatergic antidepressants with potential to treat millions of MDD sufferers worldwide who are poorly served by SSRIs, SNRIs and other current depression therapies. AV-101 is functionally similar to ketamine in that both are NMDAR antagonists. However, AV-101 modulated (down-regulated) NMDAR channel activity and ketamine blocks it. AV-101 accomplishes this NMDAR modulation by selectively binding to the functionally-required GlyB site of the NMDAR, thus down-regulating the NMDAR in a dose-dependent manner. We believe targeting the GlyB site of the NMDAR and modulating NMDAR activity rather than blocking it can bypass adverse effects that result when ketamine blocks the NMDA ion channel, without affecting the robust efficacy observed in previous clinical studies conducted by the NIH and others using ketamine to treat MDD. This NMDAR modulation by AV-101 may then result in the "glutamate surge," and the increase in neuronal connections, that has been associated with the fast-acting antidepressant effects of ketamine.

In preclinical studies, AV-101 has demonstrated the antidepressant-like activity of ketamine, including rapid onset and long duration of effect, without ketamine's serious side effects. In two NIH-funded randomized, double-blind, placebo-controlled Phase 1 safety studies, AV-101 was safe, well-tolerated and not associated with any severe adverse events. There were no signs of sedation, hallucinations or schizophrenia-like side effects often associated with ketamine and traditional NMDAR channel blockers.

Building on over $8.8 million of prior non-dilutive funding from the NIH for preclinical and Phase 1 clinical development of AV-101, in February 2015, we entered a Cooperative Research and Development Agreement (CRADA) with the U.S. National Institute of Mental Health (NIMH). Under the CRADA, we will collaborate with Dr. Carlos Zarate and the NIMH on a Phase 2 clinical study of AV-101 in subjects with treatment-resistant MDD. Pursuant to the CRADA, this study will be conducted at the NIMH by Dr. Zarate and fully-funded by the NIH. The

primary objective of the NIH-sponsored Phase 2 study will be to evaluate the ability of AV-101 to improve overall depressive symptomatology in subjects with MDD, specifically whether subjects with MDD have a greater and more rapid decrease in depressive symptoms when treated with AV-101 than with placebo. We currently anticipate commencement of the study in the second half of 2015.

AV-101 Nonclinical Studies in Chronic Neuropathic Pain, Epilepsy, Parkinson's disease and Huntington's disease

In addition to well-established nonclinical models of depression, AV-101 nonclinical data in other CNS-related disorders support our hypothesis that it may have therapeutic and commercial potential beyond treatment of depression.

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Chronic Neuropathic Pain and Acute Tissue Injury Hyperalgesia

The effect of AV-101 on chronic neuropathic pain due to inflammation and nerve damage was assessed in rats by using the Chung nerve ligation model. AV-101 effects were compared to either saline, MK-801 or gabapentin controls. Similarly to what was observed in the formalin and thermal hyperalgesia test systems, AV-101 had a positive effect on chronic neuropathic pain in the Chung model, with no observed adverse behavioral effects. The efficacy observed for AV-101 in both the acute and chronic neuropathic pain model systems was dose dependent, and the drug response was not associated with any side effects within the range of doses administered.

The antihyperalgesic effect of AV-101 has been evaluated in two standard tissue injury model systems: inflammatory thermal hyperalgesia and the formalin paw test. AV-101 was compared to two positive controls, the classic NMDAR antagonist MK-801 (discontinued in preclinical development by Merck due to neurotoxicity) and the anticonvulsant gabapentin. A significant drug response was defined as a response that was greater than or equal to 2 standard deviations (SD) from the response produced by vehicle. Animal behavior and motor function were observed and evaluated throughout the study.

In the formalin hyperalgesia model, MK-801 caused significant spontaneous locomotor activity that prevented assessment of its analgesic activity. However, AV-101 displayed dose-dependent antihyperpathic effects in the absence of behavioral deficits for both Phase 1 (acute nociceptive pain) and Phase 2 (chronic and neuropathic pain) of hyperalgesia. In contrast, gabapentin did not have a significant anti-hyperalgesia response at any dose during Phase 1, but showed a significant positive response during Phase 2.

For the carrageenan inflammatory thermal hyperalgesia model, neither MK-801, gabapentin, nor AV-101 had an effect on acute thermal nociception, but produced a dose dependent block of the carrageenan-induced hyperalgesia that were greater than 2 SD of the vehicle: There were no behavioral changes observed at any AV-101 dose, but signs of behavioral and motor dysfunction were observed for gabapentin and MK-801 treated animals. The profile of analgesic activity observed for AV-101 in the formalin and inflammatory thermal hyperalgesia model systems supports the conclusion that AV-101 demonstrates anti-hyperalgesia activity in validated models of facilitated pain processing produced by peripheral tissue inflammation.

Epilepsy

AV-101 has been shown to protect against seizures and neuronal damage in animal models of epilepsy, providing preclinical support for its potential as a novel treatment of epilepsy. Epilepsy is one of the most prevalent neurological disorders, affecting almost 1% of the worldwide population. Approximately 2.5 million Americans have epilepsy. Nearly half of the people suffering from epilepsy are not effectively treated with currently available medications. In addition, the anticonvulsants used today can cause significant side effects, which frequently interfere with compliance.

Glutamate is a neurotransmitter that is critically involved in the pathophysiology of epilepsy. Through its stimulation of the NMDAR subtype, glutamate has been implicated in the neuropathology and clinical symptoms of the disease. In support of this, NMDAR antagonists are potent anticonvulsants. However, classic NMDAR antagonists are limited by adverse effects, such as neurotoxicity, declining mental status, and the onset of psychotic symptoms following administration of the drug. The endogenous amino acid glycine modulates glutamatergic neurotransmission by stimulating the GlyB co-agonist site of the NMDA receptor. GlyB site antagonists inhibit NMDAR function and are therefore anticonvulsant and neuroprotective. Importantly, GlyB site antagonists have fewer and less severe side effects than classic NMDAR antagonists and other antiepileptic agents, making them a safer potential alternative to, and one expected to be associated with greater patient compliance than, available anticonvulsant medications.

AV-101 has two additional therapeutically important properties as a drug candidate for treatment of epilepsy:

1. AV-101 is preferentially converted to 7-Cl-KYNA in brain areas related to neuronal injury. This is because astrocytes, which are responsible for the enzymatic transamination of 4-Cl-KYN prodrug to active 7-Cl-KYNA, are focally activated at sites of neuronal injury. Due to AV-101's highly focused site of conversion, local concentrations of newly formed 7-Cl-KYNA are greatest at the site of therapeutic need. In addition to delivering the drug where it is needed, this reduces the chance of systemic and dangerous side effects with long-term use of the drug; and

2. An active metabolite of AV-101, 4-Cl-3-hydroxyanthranilic acid, inhibits the synthesis of quinolinic acid, an endogenous NMDAR agonist that causes convulsions and excitotoxic neuronal damage.

AV-101's ability to activate astrocytes for focal delivery of an anti-epileptic principle, and its dual action as a NMDAR GlyB antagonist and quinolinic acid synthesis inhibitor, make AV-101 a potential Phase 2 development candidate for treatment of epilepsy.

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Parkinson's Disease

AV-101 has been shown to activate ventral tegmental area (VTA) dopaminergic (DA) neurons. Kynurenic acid (KYNA) is an endogenous NMDA receptor antagonist, as well as a blocker of the 7-nicotinic acid receptor. Mounting evidence suggests that this compound participates in the pathophysiology of schizophrenia. Preclinical studies have shown that elevated levels of endogenous KYNA are associated with increased firing of midbrain DA neurons. AV-101 is converted to the selective NMDAR GlyB antagonist 7-Cl-KYNA, which is 20 times more potent and selective than KYNA in binding the GlyB site. Utilizing extra cellular single unit cell recording techniques, we have shown that AV-101, which is converted to the selective NMDAR GlyB antagonist 7-Cl-KYNA, significantly increases the firing rate and percent burst firing activity of VTA DA neurons. These results have potential therapeutic implications for Parkinson's disease.

Huntington's Disease

Working together with metabotropic glutamate receptors, the NMDAR ensures the establishment of long-term potentiation (LTP), a process believed to be responsible for the acquisition of information. These functions are mediated by calcium entry through the NMDAR-associated channel, which in turn influences a wide variety of cellular components, like cytoskeletal proteins or second- messenger synthases. However, over activation at the NMDAR triggers an excessive entry of calcium ions, initiating a series of cytoplasmic and nuclear processes that promote neuronal cell death through necrosis as well as apoptosis, and these mechanisms have been implicated in several neurodegenerative diseases.

Huntington's disease (HD), a chronic neurodegenerative disorder, is caused by an expansion in the number of glutamine repeats beyond 35 at the amino terminal end of a protein termed "huntingtin." Such a mutation in huntingtin leads to a sequence of progressive cellular changes in the brain that result in neuronal loss and other characteristic neuropathological features of HD. These are most prominent in the neostriatum and in the cerebral cortex, but also observed in other brain areas.

The tissue levels of two neurotoxic metabolites of the kynurenine pathway of tryptophan degradation, quinolinic acid (QUIN) and 3-hydroxykynurenine (3-HK) are increased in the striatum and neocortex, but not in the cerebellum, in early stage HD. QUIN and 3-HK and especially the joint action of these two metabolites, have long been associated with the neurodegenerative and other features of the pathophysiology of HD. The neuronal death caused by QUIN and 3-HK is due to both free radical formation and NMDA receptor overstimulation (excitotoxicity).

Based on the hypothesis that 3-HK and QUIN are involved in the progression of HD, early intervention aimed at affecting the kynurenine pathway in the brain may present a promising treatment strategy. We believe the ability of AV-101 to reduce the brain levels of neurotoxic OUIN and to potentially produce significant local concentrations of 7-Cl-KYNA on chronic administration, presents an exciting opportunity for Phase 2 clinical investigation of AV-101 as a potential chronic treatment of HD.

Summary of Additional AV-101 Nonclinical Information

A comprehensive nonclinical pharmacology, pharmacokinetic (PK)/toxicokinetic (TK), and toxicology program has been conducted to support the clinical use of AV-101 in multiple CNS-related indications. The primary pharmacological activity of AV-101 has been investigated in a series of in vitro and in vivo studies. Pharmacology (absorption, distribution, metabolism, and excretion), PK/TK, and toxicology studies have been conducted with AV-101 in rats, dogs, and monkeys. The excellent safety profile of AV-101 was confirmed by pilot tolerability, single-dose range-finding, and repeated-dose toxicology studies in rats, dogs and monkeys. The genotoxic potential of AV-101 and its active metabolite, 7-Cl-KYNA, was assessed in multiple in vitro and in vivo genotoxicity studies

(bacterial mutation, chromosomal aberration, mouse lymphoma TK+/-, and micronucleus tests).

The behavioral effects of AV-101 assessed in a Good Laboratory Practice (GLP) Irwin test in rats show it to have no adverse effect on the CNS following single oral administration at doses up to 2,000 mg/kg. Although AV-101 inhibited the human ether à-go-go–related gene (hERG) current in a dose-dependent manner (median concentration that causes 50% inhibition for the inhibitory effect [IC50] of 70.5 μM), its active metabolite, 7-Cl-KYNA, showed no inhibitory effect on the hERG channel current. Electrocardiograms (ECGs) recorded during in vivo dog toxicology studies showed no AV-101–related adverse cardiovascular effects. Furthermore, in a pivotal GLP dog 14-day toxicology study, no treatment-related effects on ECGs, including QT interval and QTc, at dose levels up to 120 mg/kg/d. No evidence of any treatment-related adverse effects on the respiratory system has been noted with AV-101.

Oral administration of AV-101 to Sprague-Dawley rats and mice was shown to result in rapid absorption of AV-101 (rats: time to maximum plasma concentration [Tmax], approximately 0.25 to 0.5 hours), adequate bioavailability (rats: approximately 39% to 94%), and relatively short plasma elimination half-life (rats: t1/2 approximately 1 to 3 hours). Furthermore, in rats 7-Cl-KYNA was detected in the plasma and reached the maximum plasma concentration (Cmax) approximately 0.25 to 0.5 hours after oral administration, suggesting a rapid conversion of AV-101 to 7-Cl-KYNA. Pharmacokinetic (PK) analyses were conducted in many of the toxicology studies in rats, dogs, and monkeys. These analyses showed that the AV-101-related clinical signs observed in dogs (versus monkeys) were associated with a significantly higher or similar exposure (Cmax and area under the curve [AUC]; single doses [equal to or greater than 50 mg/kg]; 2,000 mg/kg in monkeys). Furthermore, although AUC and Cmax values increased non-proportionately with dose level in dogs, AUC values only marginally increased with dose in monkeys, with little change in Cmax values.

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Low levels of potential metabolites of AV-101 were detected following in vitro incubations with hepatocytes from the mouse, rat, dog, monkey, and humans. No appreciable conversion of AV-101 to D-4-Cl-KYN during these hepatocyte incubations was noted. Results from cytochrome P-450 (CYP) inhibition and induction studies showed that AV-101 was not a potent inhibitor or inducer of the human CYP isoforms evaluated.

Single-dose studies in rats and monkeys did not show clear evidence of toxicity at maximal doses of 2,000 mg/kg. In dogs, oral administration of AV-101 resulted in CNS-related clinical signs, including decreased activity, abnormal gait/stance, ataxia, and prostration.

A repeated-dose (14-day) ocular toxicity study in Sprague-Dawley rats (unpigmented) and brown Norway rats (pigmented) at dose levels up to 2,000 mg/kg/d did not reveal any signs of retinal degeneration at any dose level or rat strain. A subsequent pivotal GLP 14-day repeated-dose toxicity study in Sprague-Dawley rats showed no treatment-related ocular findings after daily dosing of AV-101 for 14 consecutive days at dose levels up to 2,000 mg/kg/d.

A GLP 14-day repeated-dose CNS toxicity study conducted in dogs, at dose levels up to 100 mg/kg/d showed no treatment-related lesions in the brain of any animal. The pivotal GLP 14-day repeated-dose toxicity study in Beagle dogs, also showed no treatment-related CNS findings after daily dosing of AV-101 for 14 consecutive days at dose levels up to 120 mg/kg/d.

The genotoxic potential of AV-101 and 7-Cl-KYNA was assessed in multiple in vitro and in vivo genotoxicity studies (bacterial reverse mutation, chromosomal aberration, mouse lymphoma TK+/-, and micronucleus tests), and the overall results confirmed that both AV-101 and 7-Cl-KYNA are not mutagenic.

A rat Olney lesion study was conducted to assess the potential CNS toxicity. No lesions were observed in the brain after a single oral dose of AV-101 at doses up to 2,000 mg/kg.

Nonclinical Pharmacology Studies

Primary Pharmacodynamics

Much of the nonclinical pharmacology information of AV-101 is derived from many published research results on L-4-Cl-KYN or 7-Cl-KYNA. Primary pharmacodynamic studies conducted in rodent models for neuropathic pain demonstrated AV-101’s antihyperalgesic activity in models of facilitated pain processing, its analgesic properties, its ability to provide neuroprotection from excitotoxic death, its ability to reduce seizures, and its activity in multiple preclinical models of depression.

Nonclinical Absorption, Distribution, Metabolism and Excretion Studies

In rats, area under the concentration-time curve from time of dosing extrapolated to infinity (AUC0-) values were proportional to dose for AV-101, but Cmax was less than proportional to dose, suggesting a saturation of absorption rate. 7-Cl-KYNA Cmax was less than proportional to dose, and generally females tended to have a higher exposure to AV-101 than males, but no sex difference was noted for 7-Cl-KYNA exposure. In the repeated-dose studies, D-4-Cl-KYN, L-4-Cl-KYN, and 7-Cl-KYNA mean area under the concentration-time curves from time of dosing to the last sampling time (AUC0-t) and AUC0- values were higher on Day 14 than on Day 1 in both sexes of most treatment groups, indicating that exposure increased following daily repeated dosing of AV-101. Sex differences were noted for D-4-Cl-KYN and L-4-Cl-KYN, with mean AUC0-t and AUC0- estimates higher in females relative to males for most treatment groups. Conversely, mean AUC0-t and AUC0- values of 7-Cl-KYNA were generally higher in males relative to females.

In dogs, AUC0- values were slightly less than proportional to dose up to 100 mg/kg AV-101 and Cmax values were less than proportional to dose, suggesting a saturation of absorption. No consistent sex differences were noted for Cmax or AUC values. AUC0- and Cmax values for 7-Cl-KYNA were less than proportional to dose. In the repeated-dose study, D-4-Cl-KYN, L-4-Cl-KYN, and 7-Cl-KYNA showed a proportional increase in Cmax with the administered dose level of AV-101 in both sexes. There was no evidence of plasma accumulation for any of the analytes. Sex differences were noted for D-4-Cl-KYN, with slightly higher mean AUC0-t and AUC0- estimates in females relative to males on Day 1 and Day 14, in all treatment groups. For 7-Cl-KYNA, mean Cmax was elevated in females relative to males at all dose levels on Days 1 and Day 14, and mean AUC0-t and AUC0- estimates were also generally higher in females relative to males at all dose levels. No clear sex differences were noted for L-4-Cl-KYN.

In monkeys, AUC0- values were relatively proportional to dose, but Cmax values were not proportional to dose (comparable or lower Cmax with increasing doses). The AUC0- and Cmax values for 7-Cl-KYNA were less than proportional to dose, and no major sex differences were noted.

Nonclinical Toxicology Studies

The safety profile of AV-101 was determined in single-dose, range-finding, and repeated-dose toxicology studies in rats and dogs, and in a single-dose study in monkeys. A GLP CNS safety pharmacology study in rats that included a microscopic evaluation for Olney lesions was also conducted. Additionally, pivotal GLP 14-day repeated-dose toxicology studies in rats and dogs have been conducted. The genotoxic potentials of AV-101 and 7-Cl-KYNA were assessed in multiple in vitro and in vivo genotoxicity studies, including bacterial reverse mutation, chromosomal aberration, mouse lymphoma TK+/-, and micronucleus tests. Neither were determined to be mutagenic.

Local tolerance studies have not been conducted with AV-101. However, no lesions in the gastrointestinal tract were observed after oral administration of AV-101 in the repeated-dose toxicity studies in the rat and dog.

Based on all these studies and in accordance with the current FDA guideline and practices for selecting the starting dose of an investigational new drug, the proposed maximum starting dose in humans will not exceed 1/10 the no observed adverse effect level (NOAEL) in the most sensitive species, determined from the results of the rat and dog 14 day repeated-dose toxicology studies. The results of the pivotal 14-day studies show the dog to be the most sensitive species. The dog NOAEL was determined to be the highest dose level (120 mg/kg/d), and therefore the maximum recommended starting dose (MRSD) would be 6.5 mg/kg (12 mg/kg/d × 0.54 [conversion factor]) or 390 mg per subject for a 60-kg person. As a further added margin of safety for the clinical use of AV-101, VistaGen applied an additional safety factor to the calculated MRSD, and set the starting dose in the proposed Phase 1a clinical trial at 0.5 mg/kg (i.e., 30 mg for 60 kg subjects).

Summary of AV-101 Phase 1 Clinical Safety Studies

The safety data from two NIH-funded AV-101 clinical safety studies indicate that AV-101 was safe and well-tolerated at all three doses tested. Overall, 57 AEs were reported by 34 subjects, with 17 AEs (29.8%) occurring in the placebo group. There was a higher rate of AEs reported from subjects that received placebo than from subjects that received AV-101. A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo. Additionally, 49 of the 57 total AEs (85.9%) were considered mild, and the remaining 8 AEs (14.0%) were considered moderate. Of these AEs, headache was the most commonly reported preferred term. All of the AEs were completely resolved.

Overall, the safety results indicate AV-101 is safe and well-tolerated in healthy subjects. Subjects receiving AV-101 reported a lower percentage of AEs relative to subjects receiving placebo. Moreover, there were no AEs reported by subjects that received AV-101 that were graded as probably related to study drug. The type and distribution of AEs reported by subjects in this study was considered to be typical for a study in healthy volunteers.

A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo. The frequency of AEs was similar among the treatment groups. Thirty-four subjects experienced a total of 57 AEs, with 16 (28.1% of the total AEs) in the 360-mg group, 14 (24.6% of the total AEs) in the 1,040-mg group, 10 (17.5% of the total AEs) in the 1,440-mg group, and 17 (29.8% of the total AEs) in the placebo group. All of the AEs were completely resolved.

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/57) of the subjects receiving AV-101 and none of the 31 subjects receiving placebo reported “feelings of well-being” (coded as euphoric mood), similar to the fast-acting antidepressant effects reported in the literature with ketamine.

Phase 1 Clinical Trials

Phase 1a Study (VSG-CL-101)

A phase 1a, randomized, double-blind, placebo-controlled study to evaluate the safety and pharmacokinetics of single doses of AV-101 in healthy volunteers was conducted (VSG-CL-001). Seven cohorts (30, 120, 360, 720, 1,080, 1,440, and 1,800 mg) with six subjects per cohort (1:1, AV-101: placebo) were to be enrolled in the study. For the first five cohorts (30, 120, 360, 710 and 1,080 mg) only two subjects were dosed at a time as a pair (1:1, AV-101: placebo) on Day 1. The safety and tolerability of AV-101 in each pair of subjects was assessed by the investigator before proceeding to the next pair within the dose cohort of the study. If no safety concerns were found after analysis of the laboratory samples, physical assessments, and results of the neurological and ophthalmological examinations, the next two subjects in the cohort were dosed, but no sooner than 48 hours after the previous pair of subjects. The next cohort was dosed when the investigator and medical monitor agreed that it was safe to proceed based on review of the previous dose group's preliminary safety information. In addition, PK assessments were to be reviewed for each cohort starting with the 720 mg through the 1,800 mg dose cohort. A minimum of four evaluable subjects (two AV-101 and two placebo) were required for determination of tolerability and safety of a dose level. The PK stopping criteria would be reached when the L-4-C1-KYN mean AUC0-t reaches 900,486 ng·h/mL, or a mean Cmax of 81,633 ng/mL, or a PK extrapolation predicts exceeding one of these values in the next cohort.

All the subjects from the 1,440 mg cohort were dosed during a single day (3 subjects receiving active drug and 3 subjects receiving placebo). The safety and tolerability of AV-101 in the 1,440 mg dose cohort was to be assessed by the investigator and medical monitor before proceeding to the 1,800 mg dose cohort. If no safety concerns were found after analysis of the laboratory samples including the PK results, physical assessments, and results of the neurological and ophthalmological examinations for the 1,440 mg cohort, the 1,800-mg cohort was to be dosed. However, the PK stopping criteria were reached at the 1,440-mg cohort, and the study was stopped and did not proceed to the planned 1,800 mg cohort.

Phase 1a Study Pharmacokinetics Summary

Validated bioanalytical methods were used to measure plasma analyte concentrations. These assays had lower limits of quantification of 2 ng/mL for 7-Cl-KYNA and 5 ng/mL for L-4-Cl-KYN and D-4-Cl- KYN. Pharmacokinetic parameters were calculated by using WinNonlin Pro v. 5.2. Parameters calculated included observed maximal concentration (Cmax), observed time to Cmax (Tmax), area under the concentration-time curve to the last sample collected (AUC0-t) or extrapolated to infinity (AUC0-), and half-life (t1/2). Concentrations of all three analytes were measurable in both plasma and urine after administration of each of the six dose levels: 30, 120, 360, 720, 1,080 and 1,440 mg.

Concentration-time data were obtained after dosing of the six cohorts. Three subjects received AV-101 and three received placebo in each cohort. Plasma concentrations of L-4-Cl-KYN (AV-101) and 7-Cl-KYNA were obtained in addition to urine concentrations of these two analytes. Plasma and urine concentrations of D-4-Cl-KYN also were determined, but will be reported only for the first two cohorts.

This study was conducted under dose escalation stopping criteria as determined by the FDA of L-4-Cl-KYN mean Cmax and AUC limits of 81,633 ng/mL and 900,486 ng·h/mL, respectively. Although these criteria were not met for the mean data of the 1,440-mg dose, one subject had a Cmax that was slightly greater than the limit of 81,633 ng/mL. Therefore, dose escalation to the planned seventh cohort of 1,800 mg of AV-101 did not occur in this study. However, from a safety perspective, a maximum tolerable dose was not achieved. Also, maximum AUC values at the highest dose level remained substantially lower than the limit.

Concentrations of all three analytes were measurable in both plasma and urine after administration of all dose levels, although many of the samples from the 30-mg dose group had concentrations below the limit of quantification for 7-Cl-KYNA. Plasma concentration-time profiles were consistent with rapid absorption of the oral dose and first-order elimination. The plasma concentration-time profiles were well defined for L-4-Cl-KYN at all dose levels. Maximum concentrations occurred fairly rapidly, with individual values of Tmax ranging from 0.5 to 2 hours, with greater values tending to be in the higher dose groups. Individual t1/2 values were fairly consistent within cohorts, and mean values ranged from 1.80 to 3.33 hours. Mean t1/2 values also tended to increase with increasing dose. Mean Cmax and AUC0- values appeared to be approximately dose proportional except for those of the highest dose group.

The 7-Cl-KYNA plasma concentration-time profiles were not well defined for the 30-mg dose. Most samples for the 30-mg dose cohort had concentrations below the lower limits of quantification, and t1/2 values could not be calculated; however, profiles were sufficient after the 120-mg and greater doses to calculate all parameters.

In general, 7-Cl-KYNA maximum concentrations occurred at the same time or later than those for L-4-Cl-KYN, as may be expected since 7-Cl-KYNA is a metabolite of L-4-Cl-KYN. Individual values of Tmax ranged from 0.5 to 2 hours for both analytes. Individual 7-Cl-KYNA t1/2 values were fairly consistent within cohorts, and mean values ranged from 2.17 to 3.19 hours. Mean t1/2 values did not appear to be dose-related. Mean 7-Cl-KYNA Cmax values were somewhat dose proportional for the two initial dose groups, but tended to increase in a more than dose-proportional manner. Similarly, mean 7-Cl-KYNA AUC0-t values for all dose groups and AUC0- values for dose groups of 120 mg or greater tended to increase in a more than dose-proportional manner. Mean plasma concentrations of L-4-Cl-KYN (Figure 1) and 7-Cl-KYNA (Figure 2) are depicted for all six cohorts.

As with the 120-mg dose cohort, the plasma concentration-time profiles were well defined for both L-4-Cl-KYN and 7-Cl-KYNA at the four higher dose levels. Interestingly, the mean concentration-time profiles suggest that maximum concentrations were lower than expected, particularly for 7-Cl-KYNA.

Figure-1. Mean plasma concentrations of L-4-Cl-KYN after oral administration of a single dose of AV-101.

Figure 2. Mean plasma concentrations of 7-Cl-KYNA after oral administration of a single dose of AV-101.

Assessment of Dose Proportionality

For L-4-Cl-KYN, mean Cmax and AUC0- values appeared to be approximately dose proportional except for those of the highest dose group. These values are presented by dose in Figure 3 (Cmax) and in Figure 5-4 (AUC0-) below. Figure 3 indicates that for L-4-Cl-KYN the mean Cmax values are approximately dose linear and proportional up to a dose of 1,080 mg of AV-101. After a dose of 1,440 mg, the mean Cmax values increased only 8.8% while the dose increased by 33.3%. This is evident in the deviation of the graph from linearity at the highest dose.

Although the L-4-Cl-KYN mean Cmax values were not linear after the 1,080-mg dose, AUC0- values are approximately linear and dose proportional throughout the dose range. The nonlinearity of Cmax values at the highest dose could be a result of an outlier or simply variability in a small number of subjects (Cmax values of 44,600, 54,900, and 89,500 ng/mL were observed after the dose of 1,040-mg AV-101), it suggests that the rate or extent of absorption could be limited. The fact that AUC0- values were linear throughout the dose range suggests that the extent of absorption was not a limitation, but the rate of absorption may be limited at doses above 1,080 mg.

The lack of linearity of the L-4-Cl-KYN mean Cmax values would be expected to have a similar effect on the 7-Cl-KYNA mean Cmax values. Similarly, because the extent of absorption of L-4-Cl-KYN was linear throughout the dose range, exposure to 7-Cl-KYNA would be expected to also be linear. Mean values of 7-Cl-KYNA are presented by dose in Figure 5 (Cmax) and in Figure 5-6 (AUC0-).

gure 3. Mean Cmax values of L-4-Cl-KYN by dose of AV-101.

Figure 4. Mean AUC0- values of L-4-Cl-KYN by dose of AV-10

gure 5. Mean Cmax values of 7-Cl-KYNA by dose of AV-101.

Figure 6. Mean AUC0- values of 7-Cl-KYNA by dose of AV-101

Phase 1a Safety Summary

Nine subjects experienced 10 AEs, with four of the AEs occurring in subjects in the placebo group and two of the AEs occurring for one subject receiving 30 mg AV-101. For the AEs occurring in the AV-101–treated subjects, there were no meaningful differences in the number of AEs observed at the 30-mg dose (2 AEs) when compared with that at the 120-mg dose (1 AE), 360-mg dose (1 AE), 720-mg dose (0 AEs), 1,080-mg dose (0 AEs), or 1,440-mg dose (2 AEs). Eight of 10 AEs (80%) were considered mild, and two (20%, headache and gastroenteritis) were considered moderate. Four subjects on AV-101, one each in Cohorts 1 through 4 and two subjects on placebo in Cohort 5 reported AEs of headaches. Five headaches were mild with no concomitant treatment, and one was moderate with concomitant drug therapy administered. Most completely resolved the same day as onset and were considered not serious. One headache started the day after dosing and resolved approximately one week later on the same day as the concomitant drug therapy was administered. One case of contact dermatitis bilateral lower extremities was reported in Cohort 2 on placebo that was ongoing. One of the subjects with the headache also reported an AE of gastroenteritis that was unrelated to AV-101. This AE was considered moderate but did not require any drug therapy and was completely resolved within 2 days of onset. This AE was also considered not serious.

Even though these safety studies were not designed to quantitatively assess effects on mood, during the interviews 2 out of 3 subjects who received the highest dose (1440 mg) of AV-101, voluntarily acknowledged positive effects on mood. Similar comments were not made by any of the 18 placebo group subjects. One incident lasted approximately 15 minutes after study drug dosing, and the other event of euphoria lasted approximately 3 hours after study drug dosing. There were no other reported AEs for this cohort. The events resolved and were considered not serious.

Table 1. Summary of Adverse Events, Phase 1a

	Cohorts (mg)							
MedDRA SOC and Preferred Term	Placebo (n = 18)	30 (n = 3)	120 (n = 3)	360 (n = 3)	720 (n = 3)	1,080 (n = 3)	1,440 (n = 3)	Overall (n = 36)
Infections and Infestations	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.8%)
Gastroenteritis	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.8%)
Nervous System Disorders	1 (5.6%)	1 (33.3%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (8.3%)
Headache	1 (5.6%)	1 (33.3%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (8.3%)
Psychiatric Disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (66.7%)	2 (5.6%)
Euphoric mood	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (66.7%)	2 (5.6%)
Skin and Subcutaneous Tissue Disorder	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dermatitis contact	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.

Phase 1b Study (VSG-CL-102)

A Phase 1b clinical study was conducted as a single-site, dose-escalating study to evaluate the safety, tolerability, and PK of multiple doses of AV-101 administered daily in healthy volunteers. The antihyperalgesic effect of AV-101 on capsaicin-induced hyperalgesia was also assessed. Subjects were sequentially enrolled into one of three cohorts (360 mg, 1,080 mg, and 1,440 mg) and were randomized to AV-101 or placebo at a 12:4 (AV-101 to placebo) ratio. Subjects were to have been dosed for 14 consecutive days. Each subject was given a paper diary and instructed to record daily dose administration, concomitant medications, and AEs during the 14-day treatment period.

The safety and tolerability of AV-101 were assessed by evaluating AEs and by physical examinations, vital signs, and clinical laboratory tests (chemistry and hematology assessments) that were performed on Days 1, 7 (±1 day), and 14. Blood sampling for PK was performed on Days 1, 2, 14, and 15. Additionally, ophthalmological examinations were performed at screening and Day 15. Physical examinations, including vital signs, 12-lead electrocardiograms (ECGs), neurocognitive tests, and ataxia tests were performed on Day 1 and Day 14. Before proceeding to the next higher dose, the following criteria were met:

- Blinded safety and tolerability data were reviewed and assessed as being satisfactory by the investigator and medical monitor.

- PK assessments were reviewed by the blinded Cato Research PK specialist to determine if the PK stopping criteria were reached.

The doses evaluated in this Phase 1b multi-dose study of AV-101 were based on results obtained in a previously conducted Phase 1a single-dose study of AV-101 in healthy adults. The dose-escalation design was consistent with a standard scheme, and careful monitoring occurred to ensure the safety of all subjects.

The minimum toxic dose was defined as the dose at which the stopping criteria were reached. For this study, the minimum toxic dose was to be (1) the dose at which a drug-related serious adverse event (SAE) occurred in an AV-101–treated subject, or (2) the dose at which a severe AE that warranted stopping the study, as determined by the investigator and medical monitor, occurred in an AV-101–treated subject within a cohort. The minimum toxic dose was not reached in this study.

A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo (Table 5-6). The frequency of AEs was similar among the treatment groups. Thirty-four subjects experienced a total of 57 AEs, with 16 (28.1% of the total AEs) in the 360-mg group, 14 (24.6% of the total AEs) in the 1,040-mg group, 10 (17.5% of the total AEs) in the 1,440-mg group, and 17 (29.8% of the total AEs) in the placebo group. All of the AEs were completely resolved.

Table 2. Summary of Adverse Events (Phase 1b)

·Dose Cohorts

·	360 mgAV-101 N = 12) [n (%)]	·	1,080 mg AV-101 N = 13) [n (%)]	·	1,440 mg AV-101 (N = 12) [n (%)]