VistaGen Therapeutics, Inc.
Form S-1
October 18, 2017

As filed with the Securities and Exchange Commission on October 18, 2017

Registration No. 333-_____

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

VISTAGEN THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Nevada	3841	20-5093315
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

VistaGen Therapeutics, Inc.
343 Allerton Avenue
South San Francisco, CA 94080
(650) 577-3600
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Shawn K. Singh
Chief Executive Officer
VistaGen Therapeutics, Inc.
343 Allerton Avenue
South San Francisco, CA 94080
(650) 577-3600
(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies of all communications to:

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Approximate date of commencement of proposed sale to the public: As soon as practicable after this registration statement becomes effective.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act, check the following box. [ ]

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. [ ]

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. [ ]

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. [ ]

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,” “smaller reporting company” and “emerging growth company” in Rule 12b-2 of the Exchange Act.

Large accelerated filer	[ ]	Accelerated filer	[ ]
Non-accelerated filer	[ ]	Smaller reporting company	[X]
(Do not check if a smaller reporting company)		Emerging growth company	[ ]

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. [ ]

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Proposed maximum aggregate offering price (1)	Amount of registration fee
Common stock, $0.001 par value (1)	$23,000,000	$2,863.50

(1) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended. Includes a base offering of $20,000,000 of shares of common stock and $3,000,000 of shares of common stock subject to the underwriter's over-allotment option.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this preliminary prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities nor does it seek an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

PRELIMINARY PROSPECTUS SUBJECT TO COMPLETION DATED OCTOBER 18, 2017

Shares

Common Stock

We are offering shares of common stock.

Our common stock is presently traded on the NASDAQ Capital Market under the symbol "VTGN." On October 18, 2017, the last reported sale price of our common stock was $1.30 per share.

Investing in our securities involves risks. See "Risk Factors" beginning on page 7 of this prospectus.

	Per Share	Total
Public offering price	$	$
Underwriting discount (1)	$	$
Proceeds, before expenses, to us	$	$

(1) Please see the section titled "Underwriting" beginning on page 105 of this prospectus for additional information regarding the total compensation to be received by the underwriter.

We have granted the underwriter a 30-day option to purchase up to additional shares of our common stock on the same terms and conditions described herein, solely to cover over-allotments, if any.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The underwriter expects to deliver the shares of common stock against payment on or about , 2017.

Oppenheimer & Co.

The date of this prospectus is , 2017

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ABOUT THIS PROSPECTUS

Neither we nor the underwriter have authorized anyone to provide you with information that is different from that contained in this prospectus or in any free writing prospectus we may authorize to be delivered or made available to you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We and the underwriter are offering to sell shares of common stock and seeking offers to buy shares of common stock only in jurisdictions where offers and sales are permitted. The information contained in this prospectus is accurate only as of the date on the front of this prospectus, regardless of the time of delivery of this prospectus or any sale of shares of our common stock.

Neither we nor the underwriter have done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than the U.S. You are required to inform yourself about, and to observe any restrictions relating to, this offering and the distribution of this prospectus.

This prospectus includes industry and market data that we obtained from industry publications, internal estimates and other third-party sources. These sources may include government and industry sources. Industry publications and surveys generally state that the information contained therein has been obtained from sources believed to be reliable. Although we believe the industry and market data to be reliable as of the date of this prospectus, this information could prove to be inaccurate. Industry and market data could be wrong because of the method by which sources obtained their data and because information cannot always be verified with complete certainty due to the limits on the availability and reliability of raw data, the voluntary nature of the data gathering process and other limitations and uncertainties. In addition, we do not know all of the assumptions regarding general economic conditions or growth that were used in preparing the forecasts from the sources relied upon or cited herein.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to the registration statement of which this prospectus forms a part were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

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PROSPECTUS SUMMARY

This summary highlights information contained elsewhere in this prospectus and does not contain all of the information you should consider in making your investment decision. Before deciding to invest in our common stock, you should read this entire prospectus carefully, including the sections of this prospectus entitled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our consolidated financial statements and related notes contained elsewhere in this prospectus. Unless the context otherwise requires, the words “VistaGen Therapeutics, Inc.” “VistaGen,” “we,” “the Company,” “us” and “our” refer to VistaGen Therapeutics, Inc., a Nevada corporation. “VistaStem Therapeutics, Inc.” and “VistaGen California” refers to our wholly owned subsidiary, VistaGen Therapeutics, Inc., a California corporation doing business as VistaStem Therapeutics, Inc.

Business Overview

We are a clinical-stage biopharmaceutical company focused on developing new generation medicines for depression and other central nervous system (CNS) disorders. Unless the context otherwise requires, the words “VistaGen Therapeutics, Inc.” “VistaGen,” “we,” “the Company,” “us” and “our” refer to VistaGen Therapeutics, Inc., a Nevada corporation. All references to future quarters and years in this prospectus refer to calendar quarters and calendar years, unless reference is made otherwise.

AV-101 is our oral CNS product candidate in Phase 2 clinical development in the United States, initially as a new generation adjunctive treatment for Major Depressive Disorder (MDD) in patients with an inadequate response to standard antidepressants approved by the U.S. Food and Drug Administration (FDA). AV-101’s mechanism of action (MOA) involves both NMDA (N-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors in the brain responsible for fast excitatory synaptic activity throughout the CNS. AV-101’s MOA is fundamentally differentiated from all FDA-approved antidepressants, as well as all atypical antipsychotics,

such as aripiprazole, often used adjunctively to augment them. We believe AV-101 also has potential as a non-opioid treatment alternative for neuropathic pain, as well as several additional CNS indications where modulation of the NMDA receptors, activation of AMPA pathways and/or key active metabolites of AV-101 may achieve therapeutic benefit, including Parkinson's disease levodopa -induced dyskinesia (PD LID), epilepsy and Huntington's disease.

Clinical studies conducted at the U.S. National Institute of Mental Health (NIMH), part of the U.S. National Institutes of Health (NIH), by Dr. Carlos Zarate, Jr., Chief of the NIMH's Experimental Therapeutics & Pathophysiology Branch and its Section on Neurobiology and Treatment of Mood and Anxiety Disorders, have focused on the antidepressant effects of ketamine hydrochloride injection (ketamine), an ion-channel blocking NMDA receptor antagonist approved by the FDA as an anesthetic, in MDD patients with inadequate responses to multiple standard antidepressants. These NIMH studies, as well as clinical research at Yale University and other academic institutions, have demonstrated ketamine's robust antidepressant effects in treatment-resistant MDD patients within twenty-four hours of a single sub-anesthetic dose administered by intravenous (IV) injection.

We believe orally-administered AV-101 may have potential to deliver ketamine-like antidepressant effects without ketamine's psychological and other negative side effects. As published in the October 2015 issue of the peer-reviewed, Journal of Pharmacology and Experimental Therapeutics, in an article titled, The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition, using well-established preclinical models of depression, AV-101 was shown to induce fast-acting, dose-dependent, persistent and statistically significant antidepressant-like responses following a single treatment. These responses were equivalent to those seen with a single sub-anesthetic control dose of ketamine. In addition, these studies confirmed that the fast-acting antidepressant effects of AV-101 were mediated through both inhibiting the GlyB site of the NMDA receptor and activating the AMPA receptor pathway in the brain.

Pursuant to our Cooperative Research and Development Agreement (CRADA) with the NIMH, the NIMH is

funding, and Dr. Zarate, as Principal Investigator, and his team are conducting, a small Phase 2 clinical study of AV-101 as a monotherapy in subjects with treatment-resistant MDD (the NIMH AV-101 MDD Phase 2 Monotherapy Study). We are preparing to launch in the first quarter of 2018 a 180-patient Phase 2 multi-center, multi-dose, double blind, placebo-controlled efficacy and safety study of AV-101 as a new generation adjunctive treatment of MDD in adult patients with an inadequate response to standard, FDA-approved antidepressants (the AV-101 MDD Phase 2 Adjunctive Treatment Study). Subject to completion of this offering and the FDA's approval of our efforts to satisfy certain regulatory requirements described more fully below, we intend to launch the AV-101 MDD Phase 2 Adjunctive Treatment Study in the first quarter of 2018. Dr. Maurizio Fava, Professor of Psychiatry at Harvard Medical School and Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute, will be the Principal Investigator of our AV-101 MDD Phase 2 Adjunctive Treatment Study. Dr. Fava was the co-Principal Investigator with Dr. A. John Rush of the STAR*D study, the largest clinical trial conducted in depression to date, whose findings were published in journals such as the New England Journal of Medicine (NEJM) and the Journal of the American Medical Association (JAMA). We expect to complete this study by the end of 2018, with top line results available in the first quarter of 2019.

VistaStem Therapeutics (VistaStem) is our wholly owned subsidiary focused on applying human pluripotent stem cell (hPSC) technology to discover, rescue, develop and commercialize (i) proprietary new chemical entities (NCEs) for CNS and other diseases and (ii) regenerative medicine (RM) involving hPSC-derived blood, cartilage, heart and liver cells. Our internal drug rescue programs are designed to utilize CardioSafe 3D, our customized cardiac bioassay system, to develop small molecule NCEs for our pipeline. To advance potential RM applications of our cardiac stem cell technology, in December 2016, we exclusively sublicensed to BlueRock Therapeutics LP, a next generation RM company established by Bayer AG and Versant Ventures (BlueRock Therapeutics), rights to certain proprietary technologies relating to the production of cardiac stem cells for the treatment of heart disease (the BlueRock Agreement). In a manner similar to our exclusive sublicense agreement with BlueRock

Therapeutics, we may pursue additional RM collaborations or licensing transactions involving blood, cartilage, and/or liver cells derived from hPSCs for (A) cell-based therapy, (B) cell repair therapy, and/or (C) tissue engineering.

AV-101 and Major Depressive Disorder

Background

The World Health Organization (WHO) estimates that 300 million people worldwide are affected by depression. According to the NIH, major depression is one of the most common mental disorders in the U.S. The NIMH reports that, in 2014, approximately 16 million adults in the U.S. had at least one major depressive episode in the past year. According to the U.S. Centers for Disease Control and Prevention (CDC) one in 10 Americans over the age of 12 takes a standard, FDA-approved antidepressant.

Most standard antidepressants target neurotransmitter reuptake inhibition – either serotonin (antidepressants known as SSRIs) or serotonin/norepinephrine (antidepressants known as SNRIs). Even when

effective, these standard antidepressants take many weeks to achieve adequate therapeutic effects. Nearly two out of every three drug-treated depression patients do not obtain adequate therapeutic benefit from initial treatment with a standard antidepressant. Even after treatment with many different standard antidepressants, nearly one out of every three drug-treated depression patients still do not achieve adequate therapeutic benefits from their antidepressant medication. Such patients with an inadequate response to standard antidepressants often seek to augment their treatment regimen by adding an atypical antipsychotic (drugs such as aripiprazole), despite only modest potential therapeutic benefit and the significant risk of additional side effects.

All standard antidepressants have risks of side effects, including, among others, anxiety, metabolic syndrome, sleep disturbance and sexual dysfunction. Adjunctive use of atypical antipsychotics to augment inadequately performing standard antidepressants may increase the risk of significant side effects, including, tardive dyskinesia, substantial weight gain, diabetes and

heart disease, while offering only a modest potential increase in therapeutic benefit.

AV-101

AV-101 is our oral CNS product candidate in Phase 2 development in the United States, initially focused as a new generation antidepressant for the adjunctive treatment of MDD patients with an inadequate response to standard, FDA-approved antidepressants. As published in the October 2015 issue of the peer-reviewed, Journal of Pharmacology and Experimental Therapeutics, in an article titled, “The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition,” using well-established preclinical models of depression, AV-101 was shown to induce fast-acting, dose-dependent, persistent and statistically significant ketamine-like antidepressant effects following a single treatment, responses equivalent to those seen with a single sub-anesthetic control dose of ketamine, without the negative side effects seen with ketamine. In addition, these studies confirmed that the

antidepressant effects of AV-101 were mediated through both inhibition of the GlyB site of NMDA receptors and activation of the AMPA receptor pathway in the brain, a key final common pathway feature of certain new generation antidepressants such as ketamine and AV-101, each with a MOA that is fundamentally different from all standard antidepressants and atypical antipsychotics used adjunctively to augment them.

We have completed two NIH-funded, randomized, double blind, placebo-controlled AV-101 Phase 1 safety studies. Currently, pursuant to our CRADA with the NIMH and Dr. Carlos Zarate, Jr., the NIMH is funding, and Dr. Zarate, as Principal Investigator, and his team are conducting, the NIMH AV-101 MDD Phase 2 Monotherapy Study. Although we are not involved in conducting this study, we currently anticipate that the NIMH will complete the NIMH AV-101 MDD Phase 2 Monotherapy Study during the first half of 2018.

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We are preparing to begin the AV-101 MDD Phase 2 Adjunctive Treatment Study, which will test the safety and efficacy of AV-101 as an adjunctive treatment of MDD in patients with an inadequate response to standard, FDA-approved antidepressants. Subject to completion of this offering and assuming we receive the necessary approvals from the FDA, we intend to launch the AV-101 MDD Phase 2 Adjunctive Treatment Study in the first quarter of 2018. In connection with our preparation for this study, as well as potential Phase 3 development and commercialization of AV-101, we, together with our contract manufacturing organization (CMO), developed a novel process for the production of AV-101 drug

substance. We believe our new proprietary production process will significantly improve AV-101 manufacturing efficiency, thereby reducing the current and future cost of manufacturing AV-101 drug substance and improving the yield of AV-101 drug substance manufactured. While developing our new manufacturing process, our CMO produced a batch of AV-101 drug substance that contained certain impurities not within the limits set out by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (the ICH Guidelines). The FDA routinely utilizes the ICH Guidelines as an industry standard for development stage programs such as our AV-101 Phase 2 program. Consequently, the FDA placed a clinical hold on the

launch of the AV-101 MDD Phase 2 Adjunctive Treatment Study until we either (a) further improved our AV-101 manufacturing process to remove the impurities or reduce the impurities below applicable limits in the ICH Guidelines, or (b) conducted a bridging toxicology study to qualify the impurities as safe for clinical use. In response to the FDA's requests, we did both. We further improved our AV-101 manufacturing process, produced a new batch of AV-101 drug substance using the improved process, and now have analytical results from that batch showing that the impurities were reduced to a level below the limits of the ICH Guidelines. In addition, we conducted a bridging toxicology study, the results of which confirmed that the impurities were safe for clinical use. As a result of further

refinement of our new manufacturing process and the results of the bridging toxicology study, we believe AV-101 drug substance produced using our new manufacturing method meets all applicable regulatory guidelines.

The FDA also requested additional contraceptive protection in the upcoming clinical study until we complete preclinical reproductive toxicology studies that are routinely conducted later in stages of clinical development. Although previous toxicology studies for AV-101 do not suggest any reproductive organ involvement, and we have confirmed with the FDA that our proposed study is a Phase 2 study, we have implemented additional contraceptive measures in the revised protocol for the AV-101 MDD Phase 2 Adjunctive Treatment Study

that will remain in effect until standard reproductive toxicology studies are completed in the ordinary course prior to commencement of Phase 3 development. We have confirmed with FDA that our recently implemented contraceptive measures are appropriate for the current stage of development of AV-101.

In September 2017, we requested, and were granted, a pre-IND Type A meeting with the FDA's Division of Psychiatry to discuss certain matters pertaining to our AV-101 development program and the AV-101 MDD Phase 2 Adjunctive Treatment Study. Subsequent to our Type A Meeting with the FDA, we submitted the supplemental data from our new manufacturing process, the bridging toxicology report and our study protocol, revised to address the FDA's

comments. These documents, which we believe adequately address all concerns raised by the FDA to date, are currently under review by the FDA. Although no assurances can be given, we believe the clinical hold will be lifted in the near term, allowing us to begin the AV-101 MDD Phase 2 Adjunctive Treatment Study as planned.

We believe preclinical studies and Phase 1 safety studies support our hypothesis that AV-101 also has potential as a non-opioid treatment alternative for neuropathic pain, as well as several additional CNS indications where modulation of the NMDA receptors, activation of AMPA pathways and/or key active metabolites of AV-101 may achieve therapeutic benefit, including PD LID, epilepsy, and Huntington's disease. We are beginning to plan additional Phase 2 clinical studies of AV-101 to further

evaluate its therapeutic potential beyond MDD.

CardioSafe 3D™; NCE Drug Rescue and Regenerative Medicine

VistaStem Therapeutics is our wholly owned subsidiary focused on applying hPSC technology to discover, rescue, develop and commercialize proprietary small molecule NCEs for CNS and other diseases, as well as potential cellular therapies involving stem cell-derived blood, cartilage, heart and liver cells. CardioSafe 3D™ is our customized in vitro cardiac bioassay system capable of predicting potential human heart toxicity of small molecule NCEs in vitro, long before they are ever tested in animal and human studies. Potential commercial applications of our stem cell technology platform involve using CardioSafe 3D internally for NCE drug discovery and

drug rescue to expand our proprietary drug candidate pipeline. Drug rescue involves leveraging substantial prior research and development investments by pharmaceutical companies and others related to public domain NCE programs terminated before FDA approval due to heart toxicity risks and RM and cellular therapies. To advance potential RM applications of our cardiac stem cell technology, in December 2016, we exclusively sublicensed to BlueRock Therapeutics LP, a next generation regenerative medicine company established by Bayer AG and Versant Ventures, rights to certain proprietary technologies relating to the production of cardiac stem cells for the treatment of heart disease. In a manner similar to the BlueRock Agreement, we may also pursue additional potential RM applications

using blood, cartilage, and/or liver cells derived from hPSCs for (A) cell-based therapy (injection of stem cell-derived mature organ-specific cells obtained through directed differentiation), (B) cell repair therapy (induction of regeneration by biologically active molecules administered alone or produced by infused genetically engineered cells), or (C) tissue engineering (transplantation of in vitro grown complex tissues) using hPSC-derived blood, bone, cartilage, and/or liver cells.

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