

VistaGen Therapeutics, Inc.
Form 10-K
June 24, 2016

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

Form 10-K

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

For the fiscal year ended: March 31, 2016

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
(State or other jurisdiction of
incorporation or organization)

20-5093315
(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

Title of each class	Name of each exchange on which registered
Common Stock, par value \$0.001 per share	The NASDAQ Capital Market

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

None

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the

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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 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 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.

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Forward-Looking Statements

This Annual Report on Form 10-K (Annual Report) contains forward-looking statements that involve substantial risks and uncertainties. All statements contained in this Annual Report 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, AV-101, initially as a treatment for Major Depressive Disorder (MDD), and subsequently as a treatment for additional diseases and disorders involving the Central Nervous System;

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 U.S. and foreign countries;

the performance of the U.S. National Institute of Mental Health, our third-party contract manufacturer(s), contract research organization(s) and other third-party non-clinical and clinical development collaborators and regulatory service providers;

our ability to obtain and maintain intellectual property protection for our core 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 and product candidates in development by others that are or become available for the indications that we are pursuing;

the loss of key scientific, clinical and nonclinical development, and/or management personnel, internally or 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, particularly in Part I, Item 1A, titled “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 and the documents that we have filed as exhibits to the Annual Report 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 dedicated to developing and commercializing innovative product candidates for patients with diseases and disorders involving the central nervous system (CNS). Our lead product candidate, AV-101, is a next generation, orally available prodrug candidate in Phase 2 development, initially for the adjunctive treatment of Major Depressive Disorder (MDD) in patients with an inadequate response to standard antidepressants approved by the U.S. Food and Drug Administration (FDA). We believe AV-101 may also have potential therapeutic utility in CNS indications beyond MDD, including chronic neuropathic pain, epilepsy, Huntington’s disease and Parkinson’s disease.

AV-101’s mechanism of action, as an N-methyl D aspartate receptor (NMDAR) antagonist binding selectively at the glycine binding (GlyB) co-agonist site of the NMDAR, is fundamentally differentiated from all FDA-approved antidepressants, as well as all atypical antipsychotics used adjunctively with standard, FDA-approved antidepressants.

Our ongoing Phase 2a clinical study of AV-101 in subjects with treatment-resistant MDD is being conducted and funded by the U.S. National Institute of Mental Health (NIMH) under our February 2015 Cooperative Research and Development Agreement (CRADA) with the NIMH. The first patient in this NIMH-sponsored Phase 2a study was dosed in November 2015. The Principal Investigator of the study is 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. Previous NIMH studies, including studies conducted by Dr. Zarate, have focused on the effects of low dose intravenous (I.V.) ketamine on treatment-resistant depression. These NIMH studies, as well as clinical research by others, have demonstrated robust antidepressant effects in patients with treatment-resistant MDD within hours of a single low dose of I.V. ketamine and stimulated research and development around a new generation of antidepressants with potential to deliver ketamine-like fast-acting antidepressant benefits without ketamine’s serious side effects.

We are preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard, FDA-approved antidepressants. We anticipate commencement of this multi-center, multi-dose, double blind, placebo-controlled Phase 2b efficacy and safety study at the end of the fourth quarter of 2016. Dr. Maurizio Fava, Professor of Psychiatry at Harvard Medical School and Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute and Executive Director, MGH Clinical Trials Network and Institute, will be the Principal Investigator of our Phase 2b study of AV-101 in MDD. Dr. Fava was the co-Principal Investigator with Dr. A. John Rush of the largest clinical trial ever conducted in depression, the STAR*D study, 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 anticipate top line results in this Phase 2b study in the second quarter of 2018.

In addition to clinical development of AV-101, we are focused on advancing potential commercial applications of our human pluripotent stem cell (hPSC) technology platform with respect to drug rescue programs aimed at developing proprietary small molecule new chemical entities (NCEs) for our drug candidate pipeline. We are also focused on potential regenerative medicine (RM) applications using blood, cartilage, heart and/or liver cells derived from hPSCs,

and may pursue these applications in collaboration with third-parties.

AV-101 and Major Depressive Disorder

Background

The World Health Organization (WHO) estimates that 350 million people worldwide are affected by depression. According to the U.S. National Institutes of Health (NIH) major depression is one of the most common mental disorders in the U.S. The NIMH reports that, in 2014, an estimated 15.7 million adults aged 18 or older in the U.S. had at least one major depressive episode in the past year. This represented 6.7 percent of all U.S. adults. According to the U.S. Centers for Disease Control and Prevention (CDC) one in 10 Americans over the age of 12 takes an antidepressant medication.

Most standard, FDA-approved antidepressants target neurotransmitter reuptake inhibition – either serotonin (SSRIs) or serotonin/norepinephrine (SNRIs). Even when effective, these standard depression medications take many weeks to achieve adequate antidepressant effects. Nearly two out of every three drug-treated depression patients, including an estimated 6.9 million drug-treated MDD patients in the U.S., obtain inadequate therapeutic benefit from initial treatment with a standard antidepressant. Unfortunately, even after treatment with as many as four different standard antidepressants, nearly one out of every three drug-treated depression patients do not achieve adequate therapeutic benefits. Such treatment-resistant depression patients often seek to treat their depression with non-drug-related approaches, such as Electroconvulsive Therapy (ECT), or to augment their inadequate response to standard antidepressants by adding an atypical antipsychotic (such as, for example, aripiprazole) to their treatment regimen, despite the only modest potential therapeutic benefit and significant risk of additional side effects.

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All standard antidepressants have risks of significant side effects, including, among others, potentially anxiety, metabolic syndrome, sleep disturbance and sexual dysfunction. They also have a “Black Box” warning due to risks of worsening depression and suicide in certain groups. Use of atypical antipsychotics to augment inadequately performing standard antidepressants increases the risk of serious side effects, including, potentially, tardive dyskinesia, significant weight gain, diabetes and heart disease, while offering only a modest potential increase in therapeutic benefit. Use of ECT increases the risk of serious side effects, including, headaches, tiredness, disorientation, intense sleepiness, hallucinations and long-term memory loss.

AV-101

AV-101, our orally available prodrug candidate, is in Phase 2 clinical development for the adjunctive treatment of MDD patients with an inadequate response to standard antidepressants. As published in the October 2015 issue of the peer-reviewed, *Journal of Pharmacology and Experimental Therapeutics*, in an article entitled, 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 the NMDAR antagonist ketamine. In the same preclinical studies, a standard antidepressant, the SSRI fluoxetine, did not induce rapid onset antidepressant-like responses. In addition, these studies confirmed that the fast-acting antidepressive effects of AV-101 were mediated through the GlyB site and involved the activation of a key neurological pathway, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor pathway. Activation of the AMPA receptor pathway is a common feature of fast-acting antidepressants.

Following the completion of our NIH-funded, randomized, double blind, placebo-controlled Phase 1a and Phase 1b safety studies, we are now collaborating with the NIMH in Phase 2a. Under our February 2015 CRADA, the NIMH is sponsoring, and Dr. Carlos Zarate Jr. of the NIMH as Principal Investigator is conducting, our ongoing Phase 2a efficacy and safety study of AV-101 in subjects with treatment-resistant MDD. The trial is expected to enroll 20 to 28 patients. The first patient was dosed in November 2015, and we currently anticipate receiving topline results in the second quarter of 2017.

We are preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard, FDA-approved antidepressants. We anticipate the launch of this Phase 2b study, with Dr. Maurizio Fava of Harvard Medical School serving as Principal Investigator, at the end of the fourth quarter of 2016. We anticipate top line results from this Phase 2b study in the second quarter of 2018. Although no assurances can be given, we currently estimate that AV-101 may be ready for commercialization in 2021.

Several preclinical studies support the hypothesis that AV-101 also has the potential to treat multiple additional CNS disorders and neurodegenerative diseases beyond MDD, including chronic neuropathic pain, epilepsy, Parkinson’s disease and Huntington’s disease, where modulation of the NMDAR, AMPA pathway and/or active metabolites of AV-101 may achieve therapeutic benefit.

CardioSafe 3D™; NCE Drug Rescue and Regenerative Medicine

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. Our current strategic interests involving our stem cell technology platform include (i) advancing current internal efforts focused on CardioSafe 3D drug rescue to expand our drug candidate pipeline with selected proprietary small molecule NCEs, leveraging substantial prior research and development investments by pharmaceutical companies and others related to public domain NCEs terminated before FDA approval due to heart toxicity risks and (ii) establishing collaborative

arrangements with qualified third-parties focused on regenerative medicine (RM) applications, including (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), involving hPSC-derived blood, bone, cartilage, heart and/or liver cells.

Our Strategy

Our core strategy is to develop, and commercialize innovative small molecule CNS drugs that address significant unmet medical needs. We have assembled a management team and a team of scientific, clinical, and regulatory advisors, including recognized experts in the fields of depression, multiple other CNS diseases and disorders, and stem cell biology, with significant industry and regulatory experience to lead and execute the development and commercialization of AV-101 and any additional CNS or other product candidates we may develop internally or acquire from third-parties.

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Key elements of our strategy are to:

Develop and commercialize AV-101 for depression, including, initially, as an adjunctive treatment for MDD patients with an inadequate response to standard, FDA-approved antidepressants. Under our 2015 CRADA with the NIMH, in collaboration with Dr. Carlos Zarate of the NIMH, we launched our ongoing NIMH-sponsored AV-101 MDD Phase 2a clinical study in patients with treatment resistant MDD. The first patient in this study was dosed in November 2015. We are currently preparing to launch our multi-center Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard, FDA-approved, antidepressants. We are developing AV-101 internally, and may either continue to do so through our submission of a New Drug Application (NDA) to the FDA or, prior to submitting an AV-101 NDA, collaborate with a pharmaceutical company with a strong commercial presence in depression and other CNS markets. If AV-101 is approved by the FDA and other regulatory agencies, we may collaborate with one or more pharmaceutical companies with extensive commercial capabilities in multiple depression and other CNS markets and/or contract with a specialty sales force focused primarily on psychiatrists and long-term care physicians who are high prescribers of standard antidepressants and atypical antipsychotics.

Leverage the commercial potential of AV-101 by expanding our development and commercialization programs to additional CNS-related diseases and disorders. We believe AV-101 has broad therapeutic potential. Accordingly, we may pursue clinical development and commercialization opportunities for AV-101 across a range of CNS-related indications that are underserved by currently available CNS medicines and represent significant unmet medical needs. Based on AV-101 preclinical studies, and by leveraging our successful NIH-funded AV-101 Phase 1a and 1b clinical safety studies, we may now have opportunities to expand Phase 2 development of AV-101 beyond MDD to include, among other CNS-related indications, chronic neuropathic pain, epilepsy, Huntington's disease and Parkinson's disease.

Capitalize on our drug rescue and RM opportunities using our stem cell technology. CardioSafe 3D enables us to screen NCEs in drug rescue programs intended to produce proprietary NCEs for our internal drug candidate pipeline, without incurring many of the substantial costs and risks typically inherent in new drug discovery and nonclinical drug development. We are also focused on establishing new strategic collaborations, including potential license and/or spin-off opportunities, involving potential RM applications of our stem cell platform. As most of our resources are currently focused on the clinical development of AV-101, we believe one or more strategic licensing or development collaborations and/or spin-off transactions involving RM applications of our stem cell technology platform could allow us to realize potential value from our stem cell technology platform while focusing primarily on clinical development of AV-101, other CNS drug candidates we may acquire and/or drug candidates we may develop through internal drug rescue.

Pursue in-licensing and acquisition of other product candidates for treatment of CNS-related disorders. While our resources are currently focused primarily on clinical development of AV-101 for MDD, we anticipate pursuing license or acquisition of additional CNS-related product candidates. These may be developed independently or in partnerships. We believe a diversified CNS product candidate portfolio will mitigate risks inherent in drug development and increase the likelihood of our success.

Grow our internal development pipeline through drug rescue using our stem cell technology platform. We have developed our cardiac bioassay system, CardioSafe 3D, for drug rescue applications intended to produce proprietary small molecule NCEs for our internal drug development pipeline, without incurring many of the substantial costs and risks typically inherent in new drug discovery and nonclinical drug development.

Our Product Opportunities

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

Overview and Mechanism of Action

AV-101 is an orally available, clinical-stage prodrug candidate that readily gains access to the CNS after systemic administration and is rapidly converted in the brain into its active metabolite, 7-chlorokynurenic acid (7-Cl-KYNA), a well-characterized, potent and highly selective antagonist of the NMDAR at the GlyB co-agonist site.

Current evidence suggests that AV-101's modulation of NMDAR signaling may provide fast-acting antidepressant effects in the treatment of 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.

Major Depressive Disorder

Depression is a serious medical illness that can occur at any time over a person's life. If not effectively treated, depression is likely to become a chronic disease. Just experiencing one episode of depression places an individual at a 50% risk for experiencing another episode, and further increases the chances of having more depression episodes in the future. The WHO 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 CDC, approximately one in every 10 Americans aged 12 and over takes antidepressant medication.

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While most people will experience depressed mood at some point during their lifetime, MDD is different. MDD is the chronic, pervasive feeling of apathy, 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. Depression is also associated with an increased risk of suicide.

Standard Antidepressants

For many people, depression cannot be controlled for any length of time without treatment. Standard medications available in the multi-billion dollar global antidepressant market, including commonly-prescribed SSRIs and SNRIs, have limited effectiveness, and, because of their mechanism of action, must be taken for several weeks or months before certain patients experience any significant therapeutic benefit. In addition, most standard antidepressants have an FDA-required “Black Box” safety warning due to a risk, in certain groups, of worsening depression and an increased risk of suicidal thoughts and behaviors during treatment, a property not expected to occur with AV-101. About two out of every three depression sufferers, including an estimated 6.9 million drug-treated MDD patients in the U.S., do not receive adequate therapeutic benefits from their initial treatment with a standard antidepressant, and the likelihood of achieving remission of depressive symptoms declines with each successive treatment attempt. Even after multiple treatment attempts, approximately one out of every three depression sufferers still fails to find an effective standard antidepressant. In addition, this trial and error process and the systemic effects of the various antidepressants involved, increases the risks of patient tolerability issues and serious side effects, including suicidal thoughts and behaviors in certain groups.

Augmentation Strategies for Major Depressive Disorder

For many MDD sufferers, FDA-approved antidepressants provide less than adequate therapeutic benefit. If an MDD patient fails to respond adequately to a standard antidepressant, typically (A) the dose of their current antidepressant can be adjusted, (B) a change can be made to a different antidepressant medication, or (C) the current antidepressant regimen can be augmented with another drug. Atypical antipsychotics have recently become a common focus for augmentation of inadequate standard antidepressant therapy. Although augmenting treatment-refractory or treatment-resistant depression with atypical antipsychotics may be effective as adjunctive therapy for some MDD patients, their use as augmentation therapy increases the risk of adverse effects, such as akathisia (restlessness, a feeling of inner distress or an inability to sit still), fatigue, and weight gain.

Ketamine and NIH Clinical Studies in Major Depressive Disorder

Intravenous (I.V.) ketamine hydrochloride (ketamine) is a rapid-acting general anesthetic approved by the FDA in the 1970s. The use of ketamine (an NMDA receptor antagonist which acts as an NMDA channel blocker) to treat MDD has been studied in multiple clinical trials conducted by depression experts at several clinical research centers, including the NIMH, including Dr. Carlos Zarate, Jr. is the NIMH’s Chief of Experimental Therapeutics & Pathophysiology Branch and of the Section on Neurobiology and Treatment of Mood and Anxiety Disorders and Clinical Professor of Psychiatry and Behavioral Sciences at The George Washington University. In randomized, placebo-controlled, double blind clinical trials reported by Dr. Zarate and others at the NIMH, a single low dose of I.V. ketamine (0.5 mg/kg over 40 minutes) produced robust and rapid antidepressant effects in MDD patients who had not responded to standard FDA-approved antidepressants. These results were in contrast to the very slow onset of traditional antidepressant therapies, notably SSRIs and SNRIs, that usually require many weeks or months of chronic usage to achieve similar antidepressant effects in certain patients. The potential for widespread therapeutic use of current FDA-approved I.V. ketamine, a Schedule III drug, for MDD is limited by its potential for abuse, dissociative and psychosis-like side effects and by practical challenges associated with the necessity of I.V.

administration in a medical center. Notwithstanding these limitations, however, the discovery of ketamine's fast-acting antidepressant effects, when administered in a low dose by I.V., revolutionized thinking about the current MDD treatment paradigm involving FDA-approved SSRIs and/or SNRIs, and increased interest in the development of a new generation of antidepressants with a fast-acting mechanism of action similar to ketamine's. Our orally available AV-101 is among the next generation of antidepressants with potential to deliver fast-acting ketamine-like antidepressant effects, without ketamine's side effects nor requiring I.V. administration.

AV-101 and Major Depressive Disorder

AV-101 is an orally available prodrug candidate that produces, in the brain, 7-Cl-KYNA, one of the most potent and selective antagonists of the GlyB 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 differentiated from all standard antidepressants and all atypical antipsychotics used to augment inadequate response with standard 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, but not structurally, similar to an active metabolite of ketamine in that both induce antidepressant activity via glutamatergic activation involving AMPA receptor pathways. However, because AV-101 down-regulates the NMDAR channel activity, whereas ketamine blocks it, AV-101 does not cause ketamine-like side effects, such as hallucinations. AV-101, as a prodrug, produces in the brain an antagonist that down-regulates the NMDAR by selectively binding to the functionally required GlyB site of the NMDAR. Strong experimental evidence confirms that down-regulating the NMDAR by targeting the GlyB site can produce potent antidepressive effects and bypass adverse effects that result when ketamine blocks the NMDAR ion channel. Experimental evidence supports the conclusion that this NMDAR modulation by AV-101 may then result in a glutamatergic activation that depends on the AMPA receptor pathway, resulting in an increase in neuronal connections, synaptogenesis, that has been associated with the fast-acting antidepressant effects similar to those seen with an active metabolite of ketamine.

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In recently published preclinical studies, AV-101 has demonstrated the antidepressant-like activity of ketamine, including rapid onset and extended duration of effect, without causing 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, even at the highest dose. 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 grant award funding to VistaGen from the NIH for preclinical, and Phase 1a and Phase 1b clinical development of AV-101, in February 2015, we entered into a CRADA with the NIMH. Under the CRADA, we are collaborating with Dr. Carlos Zarate and the NIMH on a Phase 2a clinical study of AV-101 as a chronic monotherapy in subjects with treatment-resistant MDD. Pursuant to the CRADA, this study is being conducted at the NIMH by Dr. Zarate and being fully-funded by the NIMH. The primary objective of the NIH-funded Phase 2a study will be to evaluate the ability of AV-101 to improve overall depressive symptoms in subjects with treatment-resistant MDD, specifically whether subjects with MDD have a greater decrease in depressive symptoms when treated with AV-101 than with placebo. The first patient in this Phase 2a study was dosed in November 2015. We anticipate top line results in this study in the second quarter of 2017.

We are currently preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. This study will be an acute adjunctive study with clinical objectives intended to further inform the ultimate clinical usage of AV-101. We anticipate the launch of this multi-center, multi-dose, double blind, placebo-controlled Phase 2b efficacy and safety study, which is expected to enroll approximately 325 patients, in the fourth quarter of 2016. The Principal Investigator of the study will be Dr. Maurizio Fava of Harvard Medical School. Dr. Fava was the co-Principal Investigator with Dr. A. John Rush of the largest clinical trial ever conducted in depression, the STAR*D study, 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 anticipate top line results in this study in the second quarter of 2018.

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

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

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 multiple models of neuropathic pain, including the Chung nerve ligation model. AV-101 effects were compared to either saline, MK-801 or gabapentin controls. 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 positive antihyperalgesic effect of in the Chung ligation model, 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 (a channel blocker 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 the vehicle only, the solution used to deliver the drugs. Animal behavior and motor function were observed and evaluated throughout the study.

In the formalin hyperalgesia model, as has been reported by others, 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.

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Epilepsy

AV-101 has been shown to protect against seizures 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.

The ability of astrocytes to respond to pathology and/or injury becoming activated resulting in an enhanced focal delivery of an anti-epileptic active metabolite of AV-101, and the dual action resulting from AV-101 as a NMDAR GlyB antagonist and quinolinic acid synthesis inhibitor, make AV-101 a potential Phase 2a development candidate for treatment of epilepsy.

Parkinson's Disease

AV-101 has been shown to activate ventral tegmental area (VTA) dopaminergic (DA) neurons. Kynurenic acid (KYNA) is an endogenous NMDAR antagonist, as well as a blocker of the alpha-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 excitotoxicity, neuronal cell death through necrosis as well as apoptosis. These mechanisms have been implicated in several neurodegenerative diseases, and typically involve dysregulation of the endogenous levels of KYNA and quinolinic acid, with a reduction of KYNA and an increase of quinolinic acid.

Huntington's disease (HD) is an inherited disorder that causes degeneration of brain cells, called neurons, in motor control regions of the brain, as well as other areas. Symptoms of the disease, which gets progressively worse, include uncontrolled movements (called chorea), abnormal body postures, and changes in behavior, emotion, judgment, and cognition. HD 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 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).

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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 QUIN and to potentially increase local concentrations of 7-CI-KYNA, presents an exciting opportunity for Phase 2a clinical investigation of AV-101 as a potential chronic treatment of the symptoms of HD.

Summary of AV-101 Nonclinical Pharmacology, Pharmacokinetic (PK)/toxicokinetic (TK), and Toxicology Programs

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. In multiple in vitro genotoxicity studies (bacterial mutation, chromosomal aberration, mouse lymphoma TK+/-, and micronucleus tests), AV-101 and its active metabolite, 7-CI-KYNA, demonstrated no genotoxic potential.

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-CI-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 [T_{max}], approximately 0.25 to 0.5 hours), adequate bioavailability (rats: approximately 39% to 94%), and plasma elimination half-life (rats: t_{1/2} approximately 1 to 3 hours). Furthermore, in rats 7-CI-KYNA was detected in the plasma and reached the maximum plasma concentration (C_{max}) approximately 0.25 to 0.5 hours after oral administration, suggesting a rapid conversion of AV-101 to 7-CI-KYNA. Pharmacokinetic 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 similar, and at some does a significantly higher, exposure. Furthermore, although AUC and C_{max} values increased non-proportionately with dose level in dogs, AUC values only marginally increased with dose in monkeys, with little change in C_{max} values.

Low levels of potential metabolites of AV-101 were detected following in vitro incubations with hepatocytes from the mouse, rat, dog, monkey, and humans, indicating little concern with liver metabolism issues. No appreciable conversion of AV-101 to D-4-CI-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 evidence of toxicity at maximal doses of 2,000 mg/kg. In dogs, consistent with the expected drug mechanism of action, oral administration of AV-101 resulted in CNS-related clinical signs, including decreased activity, abnormal gait/stance, ataxia, and prostration at the maximum tolerated dose.

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 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.

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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 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 ($AUC_{0-\infty}$) values were proportional to dose for AV-101, but C_{max} was less than proportional to dose, suggesting a saturation of absorption rate. 7-Cl-KYNA C_{max} 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, 4-Cl-KYN, and 7-Cl-KYNA mean area under the concentration-time curves from time of dosing to the last sampling time (AUC_{0-t}) and $AUC_{0-\infty}$ 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 4-Cl-KYN, with mean AUC_{0-t} and $AUC_{0-\infty}$ estimates higher in females relative to males for most treatment groups. Conversely, mean AUC_{0-t} and $AUC_{0-\infty}$ values of 7-Cl-KYNA were generally higher in males relative to females.

In dogs, $AUC_{0-\infty}$ values were slightly less than proportional to dose up to 100 mg/kg AV-101 and C_{max} values were less than proportional to dose, suggesting a saturation of absorption. No consistent sex differences were noted for C_{max} or AUC values. $AUC_{0-\infty}$ and C_{max} values for 7-Cl-KYNA were less than proportional to dose. In the repeated-dose study, D-4-Cl-KYN, 4-Cl-KYN, and 7-Cl-KYNA showed a proportional increase in C_{max} 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 AUC_{0-t} and $AUC_{0-\infty}$ estimates in females relative to males on Day 1 and Day 14, in all treatment groups. For 7-Cl-KYNA, mean C_{max} was elevated in females relative to males at all dose levels on Days 1 and Day 14, and mean AUC_{0-t} and $AUC_{0-\infty}$ estimates were also generally higher in females relative to males at all dose levels. No clear sex differences were noted for 4-Cl-KYN.

In monkeys, $AUC_{0-\infty}$ values were relatively proportional to dose, but C_{max} values were not proportional to dose (comparable or lower C_{max} with increasing doses). The $AUC_{0-\infty}$ and C_{max} 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 was 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.

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 x 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, the Company 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).

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AV-101 Phase 1 Clinical Safety Studies

Summary

The safety data from two NIH-funded AV-101 Phase 1 clinical safety studies indicate that AV-101 was safe and well tolerated in healthy subjects at all doses tested. There were no adverse effects (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 the healthy subjects in these studies were considered to be typical for studies in healthy volunteers. All AEs were completely resolved, and no Serious Adverse Events (SAEs) were reported.

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/54) of the subjects receiving AV-101 and 0% (0/30) of the 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 1a Clinical Safety Study

A Phase 1a, randomized, double blind, placebo-controlled study to evaluate the safety and PK 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 4-C1-KYN mean AUC_{0-t} reaches 900,486 ng·h/mL, or a mean C_{max} 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 by one subject in the 1,440-mg cohort, and the dosing was stopped and did not proceed to the planned 1,800 mg cohort.

Phase 1a Clinical 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-C1-KYNA and 5 ng/mL for 4-C1-KYN and D-4-C1-KYN. Pharmacokinetic parameters were calculated by using WinNonlin Pro v. 5.2. Parameters calculated included observed maximal concentration (C_{max}), observed time to C_{max} (T_{max}), area under the concentration-time curve to the last sample collected (AUC_{0-t}) or extrapolated to infinity (AUC_{0-∞}), and half-life (t_{1/2}). 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 4-Cl-KYN 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 4-Cl-KYN mean C_{max} 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 C_{max} 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 4-Cl-KYN at all dose levels. Maximum concentrations occurred fairly rapidly, with individual values of T_{max} ranging from 0.5 to 2 hours, with greater values tending to be in the higher dose groups. Individual t_{1/2} values were fairly consistent within cohorts, and mean values ranged from 1.80 to 3.33 hours. Mean t_{1/2} values also tended to increase with increasing dose. Mean C_{max} and AUC₀₋ values appeared to be approximately dose proportional except for those of the highest dose group.

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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 $t_{1/2}$ 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 4-Cl-KYN, as may be expected since 7-Cl-KYNA is a metabolite of 4-Cl-KYN. Individual values of T_{max} ranged from 0.5 to 2 hours for both analytes. Individual 7-Cl-KYNA $t_{1/2}$ values were fairly consistent within cohorts, and mean values ranged from 2.17 to 3.19 hours. Mean $t_{1/2}$ values did not appear to be dose-related. Mean 7-Cl-KYNA C_{max} 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 AUC_{0-t} values for all dose groups and AUC_{0-} values for dose groups of 120 mg or greater tended to increase in a more than dose-proportional manner. Mean plasma concentrations of 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 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.

Assessment of Dose Proportionality

For 4-Cl-KYN, mean C_{max} and AUC_{0-} values appeared to be approximately dose proportional except for those of the highest dose group. These values are presented by dose in Figure 3 (C_{max}) and in Figure 4 (AUC_{0-}) below. Figure 3 indicates that for 4-Cl-KYN the mean C_{max} 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 C_{max} 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 4-Cl-KYN mean C_{max} values were not linear after the 1,080-mg dose, AUC_{0-} values are approximately linear and dose proportional throughout the dose range. The nonlinearity of C_{max} values at the highest dose could be a result of an outlier or simply variability in a small number of subjects (C_{max} 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 AUC_{0-} 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 4-Cl-KYN mean C_{max} values would be expected to have a similar effect on the 7-Cl-KYNA mean C_{max} values. Similarly, because the extent of absorption of 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 (C_{max}) and in Figure 6 (AUC_{0-}).

Phase 1a Clinical Study 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.

Phase 1b Clinical Safety Study

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.

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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 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; and

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 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 2). 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. No SAEs were reported.

The majority of the reported AEs were nervous system disorders (23 subjects, 46% of subjects) and gastrointestinal disorders (7 subjects, 14.0%). The remaining AEs were classified as eye disorders (3 subjects, 6.0%); psychiatric disorders (3 subjects, 6.0%); respiratory, thoracic, and mediastinal disorders (3, 6.0%); skin and subcutaneous tissue disorders (3 subjects, 6.0%); general disorders and administration site conditions (2 subjects, 4.0%); cardiac disorders (1 subject, 2.0%); infections and infestations (1 subject, 2.0%); musculoskeletal and connective tissue disorders (1 subject, 2.0%); and renal disorders (1 subject, 2.0%).

The distribution of AEs by System Organ Class was similar among the cohorts with the exception of headaches and gastrointestinal disorders. Eight of the 18 (44.4%) reported headaches were in the placebo group, 6 (33.3%) were in the 1,080-mg group, 3 (16.7%) were in the 1,440-mg group, and 1 (5.6%) was in the 360-mg group. Three (42.9%) of the 7 reported gastrointestinal disorders were in the 360-mg group, 2 (28.6%) were in the placebo group, 1 (14.3%) was in the 1,080-mg group, and 1 (14.3%) was in the 1,440-mg group.

The determination of the relationship of the AE to the study drug was made when the data were unblinded. Ten of the 15 AEs (66.7%) that occurred in the 360-mg AV-101 group, 10 of the 14 AEs (71.4%) that occurred in the 1,040-mg AV-101 group, 7 of the 10 AEs (70.0%) that occurred in the 1,440-mg AV-101 group, and 13 of the 17 AEs (76.5%) that occurred in the placebo group were determined to be possibly related to study drug. One (5.9%) AE in the placebo group was probably related to study drug (rash around neck). Of the 57 reported AEs, 49 (85.9%) were of mild intensity and 8 (14.0%) were of moderate intensity. There were 2 moderate intensity AEs in the 360-mg AV-101 group; 1 was unrelated pain in the right foot, and 1 was a possibly related headache. All other moderate AEs occurred

in the placebo group and included nausea or vomiting (2 AEs), headache (2 AEs), and rash around the neck (1 AE). No SAEs were reported.

Even though these safety studies were not designed to quantitatively assess effects on mood, during the interviews 3 (one each in the 360, 1080, and the 1440 mg cohort) out of 36 subjects who received AV-101, voluntarily acknowledged positive effects on mood, whereas none of 12 subjects on placebo expressed similar feelings.

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Phase 1b Clinical Study Pharmacokinetics Summary

Concentration-time data were obtained after dosing of the three cohorts. Plasma concentrations of 4-Cl-KYN (AV-101) and the metabolite, 7-Cl-KYNA, were obtained from subjects that received AV-101. PK parameters were calculated by using WinNonlin Pro Version 5.3. Parameters calculated included C_{max}, T_{max}, AUC_{0-t}, AUC_{0-∞}, and t_{1/2}.

Plasma concentration-time profiles obtained for 4-Cl-KYN after administration of once-daily oral doses of 360, 1,080, or 1,440 mg AV-101 were consistent with rapid absorption of the oral dose and first-order elimination of both 4-Cl-KYN and 7-Cl-KYNA, with evidence of multicompartment kinetics, particularly for the metabolite 7-Cl-KYNA. Several subjects had plasma concentration-time profiles with a last measurable sample that appeared to be an outlier or suggested multicompartment kinetics, making it challenging to identify a terminal log-linear elimination phase. Particularly for 7-Cl-KYNA, using the last two measurable samples to calculate t_{1/2} resulted in unrealistic values for some subjects.

Plasma concentration-time profiles for 4-Cl-KYN were more consistently single compartment, but several had a subtle multicompartment appearance. To be consistent in the calculation of t_{1/2} and to report a meaningful value, the final three samples with measurable concentrations were used to calculate t_{1/2} for subjects for whom those samples appeared to be log-linear. Otherwise, the last sample was essentially treated as an outlier, and the prior samples in the log-linear phase were used to calculate t_{1/2} (these samples had a higher coefficient of determination value than the last three samples). In addition, the AUC_{0-∞} values reported are calculated using the predicted last value rather than observed.

An absolute bioavailability evaluation is not possible from the data; however, an estimate of exposure can be done by comparing the AUC at the same doses. The mean AUC_{0-∞} values in the Phase 1b study were higher at all three doses than seen in Phase 1a study, suggesting similar or even higher bioavailability than that in the Phase 1a study, i.e. ≥ 31%.

In summary, the PK of AV-101 was fully characterized across the range of doses in this study. Plasma concentration-time profiles obtained for 4-Cl-KYN (AV-101) and 7-Cl-KYNA after administration of a single and multiple, once daily oral doses of 360, 1,080, or 1,440 mg were consistent with rapid absorption of the oral dose and first-order elimination of both analytes, with evidence of multi-compartment kinetics, particularly for the metabolite 7-Cl-KYNA.

Phase 1 Clinical Safety Program - Summary

The safety data from two NIH-funded AV-101 Phase 1 clinical safety studies indicate that AV-101 was safe and well tolerated in healthy subjects at all doses tested. There were no AEs reported by subjects who received AV-101 that were graded as probably related to study drug. The type and distribution of AEs reported by subjects in the studies were considered to be typical for studies in healthy volunteers. All of the AEs were completely resolved. No SAEs were reported.

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/54) of the subjects receiving AV-101 and 0% (0/30) of the 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.

The five reports of feelings of well-being occurred in one subject each at 360 (7%, 1/15 subjects) and 1,080 mg (7%, 1/15 subjects), and three subjects at 1,440 mg (20%, 3/15 subjects) in the Phase 1a and Phase 1b clinical studies,

combined. Four of the five subjects reporting feelings of well-being did not have any other adverse experiences, and one subject (1,080 mg) also reported a mild headache. These results suggest a dose response and that AV-101 at the higher doses may lead to an increased positive mood.

Stem Cell Technology

Overview

Our stem cell technology platform is based on proprietary and licensed technologies for directing the differentiation of human pluripotent stem cells (hPSCs) and producing multiple types of mature, non-transformed, functional, adult human cells for potential drug rescue and regenerative medicine (RM) applications. .

We use our hPSC-derived heart cells (cardiomyocytes) in CardioSafe 3D™, our novel, customized in vitro bioassay system, to predict potential cardiotoxicity of drug rescue NCEs. As a result of their high purity and functionality, we believe our hPSC-derived heart cells provide potential therapeutic and commercial opportunities related to RM, including cardiac tissue engineering and cardiac cell therapy. Similarly, we believe blood, cartilage and liver cells derived from our stem cell technology provide an additional diverse range of RM opportunities.

Stem cells are the building blocks of all cells of the human body. They have the potential to develop into many different mature cell types. Stem cells are defined by a minimum of two key characteristics: (i) their capacity to self-renew, or divide in a way that results in more stem cells; and (ii) their capacity to differentiate, or turn into mature, specialized cells that make up tissues and organs. There are many different types of stem cells that come from different places in the body or are formed at different times throughout our lives, including pluripotent stem cells and adult or tissue-specific stem cells, which are limited to differentiating into the specific cell types of the tissues in which they reside. We focus exclusively on human pluripotent stem cells.

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Human pluripotent stem cells can be differentiated into all of the more than 200 types of cells in the human body, can be expanded readily, and have diverse medical research, drug discovery, drug rescue, drug development and therapeutic applications. We believe hPSCs can be used to develop numerous cell types, tissues and customized assays that can mimic complex human biology in many ways relevant to drug development and RM.

Human pluripotent stem cells are either embryonic stem cells (hESCs) or induced pluripotent stem cells (iPSCs). Both hESCs and iPSCs have the capacity to be maintained and expanded in an undifferentiated state indefinitely. We believe these features make them highly useful research and development tools and as a source of normal, functionally mature cell populations for RM applications. We use multiple types of these mature cells as the foundation to design and develop novel, customized bioassay systems to test the safety and efficacy of NCEs in vitro. These cells also have potential for diverse RM applications.

Our stem cell technology platform is based on proprietary and licensed technologies for controlling the differentiation of human pluripotent stem cells (hPSCs) and producing multiple types of mature, non-transformed, functional, adult human cells for potential drug rescue and regenerative medicine (RM) applications. .

We use our hPSC-derived heart cells (cardiomyocytes) in CardioSafe 3D™, our novel, customized in vitro bioassay system, to predict potential cardiotoxicity of drug rescue NCEs. As a result of their high purity and functionality, we believe our hPSC-derived heart cells provide potential therapeutic and commercial opportunities related to RM, including cardiac tissue engineering and cardiac cell therapy. Similarly, we believe blood, cartilage and liver cells derived from our stem cell technology provide an additional diverse range of RM opportunities.

Heart Cells (Cardiomyocytes) and CardioSafe 3D Drug Rescue

We produce fully functional, non-transformed hPSC-derived cardiomyocytes (hPSC-CMs) at a level of purity greater than 95% and with normal ratios of all important cardiac cell types. Importantly, our hPSC-CM differentiation protocols do not involve either genetic modification or antibiotic selection. This is important because genetic modification and antibiotic selection can distort the ratio of cardiac cell types and have a direct impact on the ultimate results and clinical predictivity of assays that incorporate hPSC-CMs produced in such a manner. We believe our hPSC-CMs are suitable for both drug development and RM applications.

The limitations of current preclinical drug testing systems used by pharmaceutical companies and others contribute to the high failure rate of NCEs. Incorporating novel in vitro assays using early in preclinical development offers the potential to improve clinical predictability, decrease development costs, and avoid adverse patient effects, late-stage clinical termination, and product recall from the market. In addition to normal expression all of the key ion channels of the human heart (calcium, potassium and sodium) and various cardiomyocytic markers of the human heart, our CardioSafe 3D cardiac toxicity assays screening for both direct cardiomyocyte cytotoxicity and arrhythmogenesis (or development of irregular beating patterns). We believe CardioSafe 3D is sensitive, stable, reproducible and capable of generating data enabling a more accurate prediction of the in vivo cardiac effects of NCEs than is possible with existing preclinical testing systems, particularly the hERG assay.

Limited Clinical Predictivity of the FDA-Required hERG Assay

The hERG assay, which uses either transformed hamster ovary cells or human kidney cells, is currently the only in vitro cardiac safety assay required by FDA Guidelines (ICH57B). We believe the clinical predictivity of the hERG assay is limited because it assesses only a single cardiac ion channel - the hERG potassium ion channel. It does not assess any other clinically relevant cardiac ion channels, including calcium, non-hERG potassium and sodium ion channels. Also, importantly, the hERG assay does not assess the normal interaction between these ion channels and their regulators. In addition, the hERG assay does not assess clinically relevant cardiac biological effects associated

with cardiomyocyte viability, including apoptosis and other forms of cytotoxicity, as well as energy, mitochondria and oxidative stress. As a result of its limitations, results of the hERG assay can lead to false negative and false positive predictions regarding the cardiac safety of new drug candidates.

Broad Clinical Predictivity of CardioSafe 3D

We have developed and validated two clinically relevant functional components of our CardioSafe 3D screening system to assess multiple categories of cardiac toxicities, including both direct cardiomyocyte cytotoxicity and arrhythmogenesis (or development of irregular beating patterns). The first functional component of CardioSafe 3D consists of a suite of five fluorescence or luminescence based high-throughput hPSC-CM assays. These five CardioSafe 3D assays measure five the following important drug-induced cardiac biological effects:

1. cell viability;
2. apoptosis;
3. mitochondrial membrane depolarization;
4. oxidative stress; and
5. energy metabolism disruption.

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This suite of five CardioSafe 3D cytotoxicity assays provide measurement of cardiac drug effects with high sensitivity that are consistent with expected cardiac responses to drugs in numerous classes. We believe CardioSafe 3D provides valuable and comprehensive bioanalytical tools for assessing the effects of pharmaceutical compounds on cardiac cytotoxicity and can elucidate for us specific mechanisms of cardiac toxicity, thereby laying what we believe is a novel and advantageous foundation for our CardioSafe 3D drug rescue programs.

The other component of our CardioSafe 3D assay system is a sensitive and reliable medium throughput multi-electrode array (MEA) assay developed to predict drug-induced alterations of electrophysiological function of the human heart, representing an integrated assessment of not only hERG potassium ion channel activity analogous to the FDA-mandated hERG assay but, in addition, non-hERG potassium channels, and calcium channels and sodium channels, which are well beyond the scope of the hERG assay. Functional electrophysiological assessment is a key component of CardioSafe 3D, and has been validated with reported clinical results involving twelve drugs, each with known toxic or non-toxic cardiac effects in humans.

CardioSafe 3D is capable of assessing important electrophysiological activity of drugs or new drug candidates, including spike amplitude, beat period and field potential duration. Our CardioSafe 3D MEA assay, which we refer to as ECG in a test tube™, was reproducible and consistent with the known human cardiac effects of numerous compounds studied, based on the mechanisms of action and dosage of the compounds. For instance, by using CardioSafe 3D, we were able to distinguish between the arrhythmogenic cardiac effects of terfenadine (Seldane™), withdrawn by the FDA due to cardiotoxicity, and the cardiac effects of the closely structurally-related compound, fexofenadine (Allegra™), a safe variant of terfenadine, which remains on the market. We believe our correlation data demonstrate that CardioSafe 3D provides valuable and comprehensive bioanalytical tools for in vitro cardiac safety screening, well beyond the capabilities of the hERG assay. The table below reflects the broad cardiotoxicity screening capabilities CardioSafe 3D, which we believe go far beyond what is possible to assess in vitro using the FDA-required hERG assay:

Detects cardiac effects mediated by:	hERG assay	CardioSafe 3D™
hERG potassium ion channels	ü	ü
Other potassium ion channels		ü
Calcium ion channels		ü
Sodium ion channels		ü
Interactions between ion channels		ü
Channel regulatory proteins		ü
Cell viability		ü
Apoptosis		ü
Mitochondria		ü
Energy		ü
Oxidative Stress		ü

Using Stem Cell Technology to Produce and Develop Drug Rescue NCEs

Our drug rescue activities are focused on producing for our internal pipeline proprietary, safer variants of still-promising NCEs previously discovered, optimized and tested for efficacy by pharmaceutical companies and others but terminated before FDA approval due to unexpected heart toxicity. Our current drug rescue strategy involves using CardioSafe 3D to assess the toxicity that caused certain NCEs available in the public to be terminated, and use that biological insight to produce and develop a new, potentially safer, and proprietary NCEs for our pipeline. We believe the pre-existing public domain knowledge base supporting the therapeutic and commercial potential of NCEs we target for our drug rescue programs will provide us with a valuable head start as we launch each of our drug rescue programs. Leveraging the substantial prior investments by global pharmaceutical companies and others in discovery,

optimization and efficacy validation of the NCEs we identify in the public domain is an essential component of our drug rescue strategy.

By using CardioSafe 3D to enhance our understanding of the cardiac liability profile of NCEs, biological insight not previously available when the NCEs were originally discovered, optimized for efficacy and developed, we believe we can demonstrate preclinical proof-of-concept (POC) as to the efficacy and safety of new, safer drug rescue NCEs in standard in vitro and in vivo models, as well as in CardioSafe 3D, earlier in development and with substantially less investment in discovery and preclinical development than was required of pharmaceutical companies and others prior to their decision to terminate the original NCE.

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Our goal in each drug rescue program will be to produce a proprietary drug rescue NCE and establish its preclinical POC, using standard preclinical in vitro and in vivo efficacy and safety models, as well as CardioSafe 3D. In this context, POC means that the lead drug rescue NCE, as compared to the original, previously-terminated NCE, demonstrates both (i) equal or superior efficacy in the same, or a similar, in vitro and in vivo preclinical efficacy models used by the initial developer of the previously-terminated NCE before it was terminated for safety reasons, and (ii) significant reduction of concentration dependent cardiotoxicity in CardioSafe 3D.

Strategic Development and Commercialization of Drug Rescue NCEs

Once we optimize a patentable drug rescue NCE, we intend to develop it internally to establish preclinical POC in established in vitro and in vivo efficacy and safety models, as well as in CardioSafe 3D. After we establish preclinical POC of a patentable drug rescue NCE, we will decide between continuing to develop it internally and out-licensing it to a pharmaceutical company. If we license it to the pharmaceutical company, it will be responsible for all subsequent development, manufacturing, regulatory approval, marketing and sale of the drug rescue NCE and we will generate revenue through payments to us from the license upon signing the license agreement, achievement of development and regulatory milestones, and, if approved and marketed, upon commercial sales, although no assurances can be given that we will seek and complete a partnership, or that the terms of such a beneficial arrangement will be available or offered to us.

Regenerative Medicine

We believe stem cell technology-based RM has the potential to transform healthcare in the U.S. and other established pharmaceutical markets over the next decade by providing new approaches for treating the fundamental mechanisms of disease. We currently intend to establish strategic collaborations to leverage our stem cell technology platform and intellectual property. We believe our expertise in human biology, differentiation of human pluripotent stem cells to develop functional adult human cells and tissues involved in human disease, including blood, bone, cartilage, heart and liver cells, and our expertise in designing and developing novel, customized biological assay systems with the cells we produce, for regenerative medicine purposes, including both novel human disease models for discovery of small molecule drugs with regenerative and therapeutic potential and cellular therapies. Among our key objectives will be to establish one or more RM-related collaborations designed to advance potential commercial opportunities related to RM, including (A) cell-based therapy (injection of progenitor or tissue-specific mature cells obtained through directed differentiation), (B) cell repair therapy (induction of regeneration by biologically active molecules administered alone or secreted by infused engineered cells), or (C) tissue engineering (transplantation of in vitro grown tissues), each involving hPSC-derived blood, bone, cartilage, heart and/or liver cells through nonclinical and early clinical POC studies.

Strategic Relationships

Strategic collaborations are an important cornerstone of our corporate development strategy. We believe that our strategic outsourcing model gives us flexible access to medicinal chemistry, research and development capabilities, and manufacturing, clinical development and regulatory expertise at a lower overall cost than developing and maintaining the full extent of such capabilities and expertise internally on a full-time basis. In particular, we collaborate with the types of third parties identified below for the following functions:

academic and non-profit research institutions, such as the University Health Network, the McEwen Centre for Regenerative Medicine and the Centre for the Commercialization of Regenerative Medicine for stem cell technology research, development and cell production;

contract manufacturing and manufacturing service, medicinal chemistry and process development companies, such as Norac Pharma, Pharmatek and Synterys, Inc., to design, produce and analyze AV-101 clinical trial materials and potential drug rescue NCEs; and

contract clinical development and regulatory organizations (CROs), such as Pharmaceutical Product Development, LLC, Cato Research, Ltd. and Massachusetts General Hospital Clinical Trials Network and Institute for regulatory expertise and clinical development support.

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Cato Research

Cato Research is a CRO with international resources dedicated to helping biotechnology and pharmaceutical companies navigate the regulatory approval process in order to bring new biologics, drugs and medical devices to markets throughout the world. Cato Research is one of our CROs for development of AV-101, currently focused on all chemistry, manufacturing and controls (CMC) aspects of our Phase 2 development program in MDD. Cato Research's senior management team, including co-founders Allen Cato, M.D., Ph.D. and Lynda Sutton, have over 25 years of experience interacting with the FDA and international regulatory agencies and a successful track record of product approvals.

Cato BioVentures

Cato Holding Company, doing business as Cato BioVentures, is the venture capital affiliate of Cato Research. Through strategic CRO service agreements with Cato Research, Cato BioVentures invests in therapeutics and medical devices, as well as platform technologies such as our stem cell technology platform, which its principals believe, based on their experience as management of Cato Research, are capable of transforming the traditional drug development process and the research and development productivity of the biotechnology and pharmaceutical industries.

As a result of the access Cato Research has to potential drug rescue NCEs from its biotechnology and pharmaceutical industry network, as well as Cato BioVentures' strategic long term equity interest in the Company, we believe that our relationships with Cato BioVentures and Cato Research may provide us with unique opportunities relating to our drug rescue efforts that will permit us to leverage both their industry connections and the CRO resources of Cato Research, either on a contract research basis or in exchange for economic participation rights, should we develop drug rescue NCEs internally rather than out-license them to strategic partners.

Cardiac Safety Research Consortium

We have joined the Cardiac Safety Research Consortium (CSRC) as an Associate Member. The CSRC, which is sponsored in part by the FDA, was launched in 2006 through an FDA Critical Path Initiative Memorandum of Understanding with Duke University to support research into the evaluation of cardiac safety of medical products. CSRC supports research by engaging stakeholders from industry, academia, and government to share data and expertise regarding several areas of cardiac safety evaluation, including novel stem cell-based approaches, from preclinical through post-market periods.

Cardiac Safety Technical Committee of the Health and Environmental Sciences Institute – FDA's CIPA Initiative

We have also joined the Cardiac Safety Technical Committee, Cardiac Stem Cell Working Group, and Proarrhythmia Working Group of the Health and Environmental Sciences Institute (HESI) to help advance, among other goals, the FDA's Comprehensive In Vitro Proarrhythmia Assay (CIPA) initiative, which is focused on developing innovative preclinical systems for cardiac safety assessment during drug development. HESI is a global branch of the International Life Sciences Institute (ILSI), whose members include most of the world's largest pharmaceutical and biotechnology companies.

The goal of the FDA's CIPA initiative is to develop a new paradigm for cardiac safety evaluation of new drugs that provides a more comprehensive assessment of proarrhythmic potential by (i) evaluating effects of multiple cardiac ionic currents beyond hERG and ICH S7B Guidelines (inward and outward currents), (ii) providing more complete, accurate assessment of proarrhythmic effects on human cardiac electrophysiology, and (iii) focusing on Torsades de Pointes proarrhythmia rather than surrogate QT prolongation alone.

Centre for Commercialization of Regenerative Medicine

The Toronto-based Centre for Commercialization of Regenerative Medicine (CCRM) is a not-for-profit, public-private consortium funded by the Government of Canada, six Ontario-based institutional partners and more than 20 companies representing the key sectors of the regenerative medicine industry. CCRM supports the development of foundational technologies that accelerate the commercialization of stem cell- and biomaterials-based products and therapies.

We are a member of the CCRM's Industry Consortium. Other members of CCRM's Industry Consortium include Pfizer and GE Healthcare. The industry leaders that comprise the CCRM consortium benefit from proprietary access to certain licensing opportunities, academic rates on fee-for-service contracts at CCRM and opportunities to participate in large collaborative projects, among other advantages. Our CCRM membership reflects our strong association with CCRM and its core programs and objectives, both directly and through our strategic relationships with Dr. Gordon Keller and UHN. We believe our long-term sponsored research agreement with Dr. Keller, UHN and UHN's McEwen Centre offers unique opportunities for expanding the commercial applications of our stem cell technology platform by building multi-party collaborations with CCRM and members of its Industry Consortium. We believe these collaborations have the potential to transform medicine and accelerate significant advances in human health and wellness that stem cell technologies and regenerative medicine promise.

Massachusetts General Hospital Clinical Trials Network and Institute

Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI) is an academic CRO, part of the Department of Psychiatry of the Massachusetts General Hospital (MGH), a leader in academic scientific and clinical research in psychiatry. By exploring the brain science, genetics, and neurobiology of psychiatric disorders, the MGH CTNI has been instrumental in the development of novel treatments and surrogate markers of illness and therapeutic response. Its scientific and clinical research has been instrumental in defining the standards for the state-of-the-art practice of psychiatry. We are working with MGH CTNI, including its principals, Dr. Maurizio Fava and Dr. Thomas Laughren, in connection with the planning and execution of our Phase 2b clinical study of AV-101 for treatment of MDD. Dr. Fava is acknowledged as a world renowned expert in depressive disorders and psychopharmacology. He is Director of the Division of Clinical Research of the MGH Research Institute, Executive Vice Chair, Department of Psychiatry, at MGH, and Executive Director of MGH CTNI. He will serve as Principal Investigator of our Phase 2b study of AV-101 in MDD. Dr. Laughren is the former FDA Division Director, Division of Psychiatry Products, Center for Drug Evaluation and Research (CDER).

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Pharmaceutical Product Development, LLC

Pharmaceutical Product Development, LLC (PPD) is a leading global CRO providing comprehensive, integrated drug development, laboratory and lifecycle management services. With offices in 46 countries and more than 15,000 professionals worldwide, PPD applies innovative technologies, therapeutic expertise and a firm commitment to quality to help its clients and partners bend the cost and time curve of drug development to deliver life-changing therapies that improve health. We are currently working with PPD as our full-service CRO in connection with the planning and execution of our Phase 2b clinical study of AV-101 for treatment of MDD.

Synterys, Inc.

We have entered into a strategic medicinal chemistry collaboration agreement with Synterys, Inc., a medicinal chemistry and collaborative drug discovery company. We believe this important collaboration will further our drug rescue initiatives with the support of Synterys' medicinal chemistry expertise. In addition to providing flexible, real-time contract medicinal chemistry services in support of our drug rescue programs, we anticipate potential collaborative opportunities with Synterys wherein we may jointly identify and develop drug rescue NCEs.

United States National Institutes of Health

Since our inception in 1998, the NIH has awarded us \$11.3 million in non-dilutive research and development grants, including \$2.3 million to support research and development of our stem cell technology and \$8.8 million for nonclinical and Phase 1 clinical development of AV-101.

United States National Institute of Mental Health

The U.S. National Institute of Mental Health, part of the NIH, is the largest scientific organization in the world dedicated to mental health research. NIMH is one of 27 Institutes and Centers of the NIH, the world's leading biomedical research organization. The mission of NIMH is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery and cure. In February 2015, we entered into CRADA with the NIH providing for our ongoing AV-101 Phase 2a efficacy and safety study in MDD. This Phase 2a study is being fully funded by the NIH and is being conducted at the NIMH by Dr. Carlos Zarate, the NIMH's Chief of Experimental Therapeutics & Pathophysiology Branch and Section on Neurobiology and Treatment of Mood and Anxiety Disorders.

University Health Network, McEwen Centre for Regenerative Medicine

University Health Network (UHN) in Ontario, Canada is a major landmark in Canada's healthcare system. UHN is one of the world's largest research hospitals, with major research in transplantation, cardiology, neurosciences, oncology, surgical innovation, infectious diseases and genomic medicine.

The McEwen Centre for Regenerative Medicine (McEwen Centre) is a world-renowned center for stem cell biology and regenerative medicine and a stem cell research facility affiliated with UHN. Dr. Gordon Keller, our co-founder and Chairman of our Scientific Advisory Board, is Director of the McEwen Centre. Dr. Keller's lab is considered one of the leaders in successfully applying principles from the study of developmental biology of many animal systems to the differentiation of pluripotent stem cell systems, resulting in reproducible, high-yield production of human heart, liver, blood and vascular cells. The results and procedures developed in Dr. Keller's lab are often quoted and used by academic scientists worldwide.

In September 2007, we entered into a long-term sponsored stem cell research and development collaboration with UHN. In December 2010, we extended the collaboration to September 2017. The primary goal of this ten-year collaboration is to leverage the stem cell research, technology and expertise of Dr. Gordon Keller to develop and commercialize industry-leading human pluripotent stem cell differentiation technology and bioassay systems for drug rescue and development and regenerative cell therapy applications. This sponsored research collaboration builds on our existing strategic licenses from National Jewish Health and the Icahn School of Medicine at Mount Sinai to certain pluripotent stem cell technologies developed by Dr. Keller, and is directed to diverse human pluripotent stem cell-based research projects, including, as expanded and amended, strategic projects related to drug rescue and regenerative medicine.

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Intellectual Property

We rely upon patents as a major component of our intellectual property portfolio, as is typical for development-stage, biopharmaceutical companies. In addition, from time to time, we enter into patent license agreements to acquire rights to intellectual property. We also rely, in part, on trade secrets for protection of some of our discoveries. We attempt to protect our trade secrets by entering into confidentiality agreements with employees, consultants, collaborators and third parties. We also own several registered and common-law trademarks.

To help protect our intellectual property rights, our employees and consultants also sign agreements in which they assign to us, for example, their interests in patents, trade secrets and copyrights arising from their work for us.

From time to time, we sponsor research with key scientists in academic institutions to advance or supplement our internal research and development activities and objectives. These sponsored research agreements generally provide us with an opportunity to negotiate a new license, or acquire a substantially prescribed license, to acquire intellectual property rights in the results of the sponsored research.

AV-101

As discussed elsewhere in this Annual Report, AV-101 (4-Cl-KYN) is a development-stage prodrug candidate presently being studied in an NIH-sponsored Phase 2a clinical trial for the treatment of MDD. We have developed a broad and diverse portfolio of intellectual property assets around AV-101, which involves both patent applications and trade secrets. In addition, we will seek regulatory exclusivity to supplement our intellectual property rights.

AV-101 itself is not patented. We obtained a patent license from the University of Maryland to certain pharmaceutical formulations and associated methods of using AV-101 when we acquired the original licensee, Artemis Neuroscience, Inc. Patent rights included in that license that were relevant to AV-101, however, have expired. Although the license agreement contains royalty obligations that nominally remain in force until 10 years after the first commercial sale of the first product even after relevant patent rights have expired, the U.S. Supreme Court's decision in *Kimble v. Marvel Entertainment, LLC* (2015) determined that patent license royalties that extend beyond a patent's expiration are not enforceable.

Even though the compound 4-Cl-KYN per se and certain of its formulations are in the public domain and thus are no longer protectable, we have filed several of our own patent applications on certain other formulations and novel therapeutic methods of use of AV-101 as part of our strategy to seek and secure market exclusivity.

Presently, we are prosecuting a family of patent applications in the USPTO, European Patent Office and selected major markets related to specific dosage formulations of AV-101, as well as to methods of treating depression, hyperalgesia pain and several other neurological conditions. For reference, these are based on PCT patent application WO2014/116739. We have recently filed a continuation application in this family in the U.S., focused on the treatment of depression, that is undergoing accelerated examination. There is no guarantee, however, that the USPTO will allow any of the pending claims.

We are also prosecuting a second patent family related to novel methods of synthesizing AV-101, based on extensive research involving a range of synthetic routes that was conducted on our behalf by a separate contract research organization. For reference, this is based on PCT patent application WO2014/152835, which is presently being pursued at the national phase in the U.S. and selected other countries. This patent application also includes pharmaceutical composition claims to certain compounds related to AV-101, which may be useful and patentable as synthesis intermediates.

Another patent application related to additional and expanded clinical uses of AV-101 to treat depression and other medical conditions was filed in the U.S. as a provisional application in 2015. A PCT patent application corresponding to the provisional was filed in May 2016, and we plan to seek patent protection at the national phase in appropriate global markets.

Additionally, we are presently developing potentially improved synthesis routes through another contract research organization. If we determine that these routes may be patentable, then we intend to file patent applications relating to this R&D activity in the second half of 2016.

As noted, we are involved with an ongoing Phase 2a study of AV-101 in MDD being conducted by the NIMH. As part of our analysis of the study results, we will be evaluating the possibility of seeking additional patent protection based on the clinical data and on clinical observations.

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As another major component of our plans to obtain market exclusivity for approved therapeutic indications for AV-101, we intend to utilize New Drug Product Exclusivity provided by the FDA under section 505(c)(3)(E) and 505(j)(5)(F) of the Federal Food, Drug, and Cosmetic Act (FDCA). The FDA's New Drug Product Exclusivity is available for NCEs such as AV-101, which are innovative and have not been previously approved by the FDA, either alone or in combination with other drugs. The FDA's New Drug Product Exclusivity protection provides the holder of an FDA-approved NDA with up to five years of protection from competition in the U.S. marketplace for the innovation represented by its approved new drug product. This protection precludes FDA approval of certain generic drug applications under section 505(b)(2) of the FDCA, as well as certain abbreviated new drug applications (ANDAs), during the up to five-year exclusivity period, except that such applications may be submitted after four years if they contain a certification of patent invalidity or non-infringement. We will pursue similar types of regulatory exclusivity in other regions, such as Europe, and in certain other countries.

There is no guarantee that we will be successful in obtaining patents in the U.S. or other countries related to AV-101, or that if we are successful in obtaining such patents that we would also be successful in protecting those patents against challengers or in enforcing them to stop infringement. We are pursuing patent rights in a limited number of countries that we believe are the few major markets where having patent rights will substantially facilitate commercialization of AV-101. There are many other countries in which we are not pursuing such patent rights. And there is no guarantee that we will successfully obtain patents in the countries in which we are pursuing patent rights.

Stem Cell Technology

We have obtained and are pursuing intellectual property rights to several stem cell technologies through a combination of our own patent properties, exclusive and non-exclusive patent and technology licenses, and participation in sponsored research relationships. Generally, our stem cell IP portfolio relates to drug development, drug rescue/toxicity testing, drug discovery and cell therapy. It also relates to novel production systems and the use of various cell types that have been differentiated from pluripotent stem cells for those and other purposes. Additionally, the IP includes enriched populations of certain cell types, such as cardiomyocytes and hepatocytes, and some related aspects of cell-based therapy. We also maintain certain trade secrets regarding stem cell technology.

Overall, our stem cell patent portfolio includes nine patent families, which collectively include 11 issued U.S. patents that remain in force and eight pending U.S. patent applications, as well as several foreign counterpart patents and patent applications in countries of commercial interest to VistaGen. The portfolio also includes several patent applications pending in the U.S. and in various foreign countries. For convenience of reference, our stem cell patent portfolio is based on published PCT patent applications WO 1997/021802, WO2000/034525, WO2004/098490, WO2001/096866, WO2012/024782, WO2013/075222, WO2014/124527, WO2014/161075 and WO2015035506, several of which are discussed below.

The patent properties in these families are based on discoveries from our internal research and development activities, research that we have sponsored at various academic institutions, as well as from patent license agreements signed with the National Jewish Medical and Research Center, University Health Network and the Mount Sinai School of Medicine.

These license agreements generally require us to pay annual license fees, patent prosecution and maintenance fees, and royalty payments that vary based on product sales and services that are covered by the licensed patent rights, as well as fees for sublicensing. As noted above in the context of AV-101 intellectual property, there is no guarantee that we will successfully obtain or maintain patents in the countries in which we are pursuing patent rights or that we would be successful in enforcing granted patent rights against infringers.

Trademarks

We have a U.S. federal trademark registration for the trademark “VISTAGEN”. Corresponding trademarks have been registered in the European Union and in Switzerland. We also use certain other trademarks in connection with our customized in vitro bioassay systems, such as CardioSafe 3D™, LiverSafe 3D™ and “Better Cells Lead to Better Medicine™”.

Sponsored Research Collaborations and Intellectual Property Rights

University Health Network (UHN), McEwen Centre for Regenerative Medicine, Toronto, Ontario

Our strategic relationship with our co-founder, Dr. Gordon Keller, Director of the UHN’s McEwen Centre, is focused on, among other things, developing improved methods for differentiation of cardiomyocytes (heart cells) from hPSCs, and their uses in bioassay systems for drug discovery and drug development, including drug rescue, cell therapy and regenerative medicine. Pursuant to our sponsored research collaboration agreement with UHN, we have acquired exclusive worldwide rights to patent applications in the U.S. and foreign countries on multiple inventions arising from studies we have sponsored, under pre-negotiated license terms. Such pre-negotiated terms provide for royalty payments based on product sales that incorporate the licensed technology and milestone payments based on the achievement of certain events. Any drug rescue compounds that we develop will not incorporate the licensed technology and, therefore, will not require any royalty payments. To the extent we incur royalty payment obligations from other business activities, the royalty payments will be subject to anti-stacking provisions, which reduce our payments by a percentage of any royalty payments paid to third parties who have licensed necessary intellectual property to us.

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The sponsored research collaboration agreement (SRCA) with UHN, as amended, has a term of ten years, ending on September 18, 2017. We are currently in discussions with Dr. Keller and UHN regarding the scope of potential new sponsored research projects under the SRCA. The ten-year term of the agreement is subject to renewal upon mutual agreement of the parties. The agreement may be terminated earlier upon a material breach by either party that is not cured within 30 days. UHN may elect to terminate the agreement if we become insolvent or if any license granted pursuant to the agreement is prematurely terminated. We have the option to terminate the agreement if Dr. Keller stops conducting his research or ceases to work for UHN.

UHN Licenses for Stem Cell Culture Technology

In October 2011, we licensed stem cell culture technology from UHN's McEwen Centre pursuant to Sponsored Research Collaboration Agreement (SCRA). This exclusive license conveyed rights to a patent application published as a PCT application WO/2012/024782, entitled "Methods for Enriching Pluripotent Stem Cell Derived Cardiomyocyte Progenitor Cells and Cardiomyocyte Cells Based on SIRPA Expression," and any related patent application or patent claiming priority from it. This technology involves a cell surface protein, SIRPA (signal-regulatory protein alpha), that heretofore was not known to be expressed by early immature precursors for cardiomyocytes. Antibodies and other binding moieties specific to SIRPA allow the identification and enrichment of these early cardiomyocyte precursors, which we believe will provide benefits in terms of purity, functionality and reproducibility for not only CardioSafe 3D™ in vitro safety assays for drug screening and development, but also potentially for production of cardiomyocytes for cell therapy and regenerative medicine applications.

In April 2012, we licensed additional stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. The licensed technology may be used to develop hematopoietic precursor stem cells from human pluripotent stem cells, with the goal of developing drug discovery screening and regenerative medicine applications for human blood system disorders. This exclusive license conveyed rights to a patent application published as PCT patent application WO/2013/075222, entitled "Populations of Hematopoietic Progenitors and Methods of Enriching Stem Cells Therefor," and any related patent application or patent claiming priority from it. We believe this stem cell technology substantially advances our ability to produce and purify this important blood stem cell precursor for both in vitro drug discovery screening and potential regenerative medicine applications. In addition to defining new cell culture methods for our use, the technology describes the surface characteristics of stem cell-derived adult hematopoietic stem cells. Most groups study embryonic blood development from stem cells, but we are able to not only purify the stem cell-derived precursor of all adult hematopoietic cells, but also pinpoint the precise timing when adult blood cell differentiation takes place in these cultures. We believe these early cells, isolated through our licensed technology, have the potential to be the precursors of the ultimate adult, bone marrow-repopulating hematopoietic stem cells potentially useful to repopulate the blood and immune system when transplanted into bone marrow transplantation patients. These cells have important potential therapeutic applications for the restoration of healthy blood and immune systems in individuals undergoing transplantation therapies for cancer, organ grafts, HIV infections or for acquired or genetic blood and immune deficiencies.

In December 2014, we licensed additional stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. This exclusive license conveyed rights to a patent application published as PCT patent application WO/2014/124527, entitled "Methods for Generating Hepatocytes and Cholangiocytes from Pluripotent Stem Cells," and any related patent application or patent claiming priority from it. The licensed technology describes advanced methods for the production of mature hepatocytes and cholangiocytes, the primary cell types of the liver. The liver plays an important role in many bodily functions including protein production, blood clotting, as well as glucose, iron and lipid metabolism. Hepatocytes are the major cells responsible for metabolizing drugs, drug-drug interactions, and are the target for a variety of liver diseases and disorders, including drug-induced liver failure, Cirrhosis, and viral infections. Cholangiocytes are the precursors for the biliary system found in the liver, i.e. bile ducts and gallbladder. The biliary system is a significant target for many conditions, including drug toxicities, cholecystitis, and liver-related abnormal

function associated with the cystic fibrosis mutation. We believe the licensed technology will enable us to more efficiently produce, human hepatocytes and cholangiocytes with more adult-like functions for potential drug discovery, drug rescue and regenerative medicine applications.

In December 2014, we also licensed another stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. This exclusive license conveyed rights to a patent application entitled "Methods and Compositions for Generating Epicardium Cells," published as PCT patent application WO/2015/035506, and any patent application or patent claiming priority from it. The epicardium is the outer cell layer on top of the heart muscle (cardiomyocytes), and is essential for proper development of the heart and plays an important role in cardiac recovery during disease. The epicardium plays a critical role in the differentiation, expansion, and maturation of cardiomyocytes during development, or during cardiac repair responses. This patent application also relates to the differentiation of cardiomyocytes, fibroblast-like cells and smooth muscle-like cells. This technology will be important to developing the next generation of engineered cardiac tissue and their use in cell therapy approaches.

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Also in December 2014, we licensed an additional stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. This exclusive license conveyed rights to a patent application entitled "Methods and Compositions for Generating Chondrocyte Lineage Cells and/or Cartilage Like Tissue" published as PCT patent application WO/2014/161075, and any related patent application or patent claiming priority from it. There are two types of chondrocytes, "articular" and "growth plate." Articular chondrocytes are responsible for cartilage that lines our joints, whereas growth plate chondrocytes are involved with new bone formation. Osteoarthritis is debilitating joint diseases resulting from the degeneration of the first kind, articular cartilage, leading to inappropriate bone development (spurs) in the joint. This technology will allow us to develop in vitro assays to study the process of the degeneration of articular cartilage, and it provides novel tools for testing drugs that have the potential to reduce this degeneration. It also provides the necessary cells for developing cell therapy approaches for treating osteoarthritis.

U.S. Government Rights

We have received federal funding from both the NIH and the NIMH to support research and development of inventions disclosed in certain of our patent applications relating to AV-101 and certain of our patent applications relating to stem cell technology. Under the Bayh-Dole Act of 1980, if we do not take adequate steps to commercialize certain intellectual property rights, or certain other exigent circumstances relating to public health and safety prescribed under federal law become applicable, the U.S. government may exercise certain rights reserved by statute with respect to inventions made in the course of programs funded by NIH, NIMH or other federal grants.

Competition

The biopharmaceuticals industry is highly competitive. There are many public and private biopharmaceutical companies, universities, governmental agencies and other research organizations actively engaged in the research and development of products that may be similar to our product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products will increase.

Currently, there are no FDA-approved therapies for MDD with the mechanism of action of AV-101. However, products approved for other indications, for example, low doses of the anesthetic ketamine, are being or may be increasingly used off-label for treatment-resistant MDD, as well as other CNS indications for which AV-101 may have therapeutic potential. Additionally, other treatment options, such as psychotherapy and electroconvulsive therapy, are sometimes used instead of and before antidepressant medications to treat patients with MDD.

In the field of new generation antidepressants focused on modulation of the NMDAR at its GlyB site, our principal competitor is Allergan plc, which is developing rapastinel (formerly GLYX-13) and NRX-1074 for treatment-resistant MDD. On August 28, 2015, Allergan acquired rapastinel and NRX-1074 from Naurex, Inc. (Naurex) in an all-cash transaction of \$571.7 million, plus future contingent payments up to \$1.15 billion. Although each of these drug candidates is a peptide and may not be orally active (rapastinel is only administered intravenously and, we believe, NRX-1074 has not yet been administered orally to patients), both are new generation NMDAR modulators focused on the GlyB site of the NMDAR.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. We believe that a range of pharmaceutical companies have programs to develop small molecule drug candidates for the treatment of depression, including MDD, epilepsy, neuropathic pain, Parkinson's disease and other neurological conditions and diseases, including, but not limited to, Abbott Laboratories, Acadia, Alkermes, Allergan, AstraZeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Novartis, Ono, Otsuka, Pfizer, Roche, Sanofi, Shire, Sumitomo, Takeda and Teva. Mergers and acquisitions in the biotechnology and

pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. We expect that AV-101 will have to compete with a variety of therapeutic products and procedures.

We believe that our human pluripotent stem cell (hPSC) technology platform, the hPSC-derived human cells we produce, and the customized human cell-based assay systems we have formulated and developed are capable of being competitive in the diverse and growing global stem cell and regenerative medicine markets, including markets involving the sale of hPSC-derived cells to third-parties for their in vitro drug discovery and safety testing, contract predictive toxicology drug screening services for third parties, internal drug discovery, drug development and drug rescue of new , and regenerative medicine, including in vivo cell therapy research and development. A representative list of such biopharmaceutical companies pursuing one or more of these potential applications of adult and/or hPSC technology includes the following: Acea Biosciences, Astellas, Athersys, BioCardia, BioTime, Collectis Bioresearch, Cellerant Therapeutics, Cytori Therapeutics, Fujifilm Holdings, HemoGenix, International Stem Cell, NeoStem, Neuralstem, Organovo Holdings, PluriStem Therapeutics, Stem Cells, and Stemina BioMarker Discovery. Pharmaceutical companies and other established corporations such as Bristol-Myers Squibb, GE Healthcare Life Sciences, GlaxoSmithKline, Novartis, Pfizer, Roche Holdings, Thermo Fischer Scientific and others have been and are expected to continue pursuing internally various stem cell-related research and development programs. Many of the foregoing companies have greater resources and capital availability and as a result, may be more successful in their research and development programs than us. We anticipate that acceptance and use of hPSC technology for drug development and regenerative medicine will continue to occur and increase at pharmaceutical and biotechnology companies in the future.

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Government Regulation

Government authorities in the U.S. at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

U.S. Drug Development

In the U.S., the FDA regulates drugs under the FDCA and its implementing regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the U.S.. The process required by the FDA before a drug may be marketed in the U.S. generally involves the following:

- Completion of extensive non-clinical, sometimes referred to as non-clinical laboratory tests, non-clinical animal studies and formulation studies in accordance with applicable regulations, including the FDA's current Good Laboratory Practice (cGMP), regulations;

- Submission to the FDA of an IND application, which must become effective before human clinical trials may begin;

- Approval by an independent institutional review board (IRB) or ethics committee at each clinical trial site before each trial may be initiated;

- Performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, sometimes referred to as good clinical practices (GCPs) to establish the safety and efficacy of the proposed drug for each proposed indication;

- Submission to the FDA of an NDA, for a new drug;

- A determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;

- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with cGMP requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;

- Potential FDA audit of the non-clinical and/or clinical trial sites that generated the data in support of the NDA; and

FDA review and approval of the NDA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the drug in the United States.

The non-clinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Non-clinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product.

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The data required to support an NDA is generated in two distinct development stages: non-clinical and clinical. For new chemical entities, the non-clinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the non-clinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the non-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. Some non-clinical testing may continue even after the IND is submitted, but an IND must become effective before human clinical trials may begin. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials, including subjects will be exposed to unreasonable health risks, and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent IRB at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA so long as the clinical trial is conducted in compliance with an international guideline for the ethical conduct of clinical research known as the Declaration of Helsinki and/or the laws and regulations of the country or countries in which the clinical trial is performed, whichever provides the greater protection to the participants in the clinical trial.

Clinical Trials

Clinical trials are generally conducted in three sequential phases that may overlap, known as Phase 1, Phase 2 and Phase 3 clinical trials.

Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.

Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks and preliminary evaluation of efficacy.

Phase 3 clinical trials generally involve large numbers of patients at multiple sites (from several hundred to several thousand subjects) and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product approval. Phase 3 clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing.

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Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse events, finding from other studies, or any finding from animal or in vitro testing that suggests a significant risk for human subjects. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA, the IRB, or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, we must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA Review Process

The results of non-clinical studies and of the clinical trials, together with other detailed information, including extensive manufacturing information and information on the composition of the drug and proposed labeling, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. FDA approval of an NDA must be obtained before a drug may be offered for sale in the United States.

In addition, under the Pediatric Research Equity Act (PREA) an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers.

Under the Prescription Drug User Fee Act (PDUFA) as amended, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through December 31, 2014, the user fee for an application requiring clinical data, such as an NDA, is \$2.2 million. PDUFA also imposes an annual product fee for human drugs of \$0.1 million and an annual establishment fee of \$0.6 million on facilities used to manufacture prescription drugs. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has 10 months from the filing date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the filing date for a priority NDA. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA will likely re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

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After the FDA evaluates an NDA, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, non-clinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing or clinical trials and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess a drug's safety and efficacy and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a risk evaluation and mitigation strategy (REMS) to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the U.S., or more than 200,000 individuals in the U.S. and for which there is no reasonable expectation that the cost of developing and making a drug product available in the U.S. for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication than that for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same product as defined by the FDA or if our product candidate is determined to be contained

within the competitor's product for the same indication or disease. If a drug designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs that meet certain criteria. Specifically, new drugs are eligible for Fast Track designation if they are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may review sections of the marketing application on a rolling basis before the complete NDA is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

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Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or offers a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review. A product may also be eligible for accelerated approval. Drugs studied for their safety and efficacy in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug shown to be effective can be safely used only if distribution or use is restricted, it will require such post-marketing restrictions, as it deems necessary to assure safe use of the drug, such as:

distribution restricted to certain facilities or physicians with special training or experience; or

distribution conditioned on the performance of specified medical procedures.

The limitations imposed would be commensurate with the specific safety concerns presented by the drug. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Additionally, a drug may be eligible for designation as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more indications. The benefits of breakthrough therapy designation include the same benefits as fast track designation, plus intensive guidance from FDA to ensure an efficient drug development program. Fast Track designation, priority review, accelerated approval and breakthrough designation do not change the standards for approval, but may expedite the development or approval process.

Pediatric Trials

The Food and Drug Administration Safety and Innovation Act (FDASIA) which was signed into law on July 9, 2012, amended the FDCA to require that a sponsor who is planning to submit a marketing application for a drug that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan (PSP) within sixty days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from non-clinical studies, early phase clinical trials, and/or other clinical development programs.

Post-Marketing Requirements

Following approval of a new product, a pharmaceutical company and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the

applicable regulatory authorities of adverse experiences with the product, providing the regulatory authorities with updated safety and efficacy information, product sampling and distribution requirements, and complying with promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the Internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Further, if there are any modifications to the drug, including changes in indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA or NDA supplement, which may require the applicant to develop additional data or conduct additional non-clinical studies and clinical trials. As with new NDAs, the review process is often significantly extended by FDA requests for additional information or clarification. Any distribution of prescription drug products and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act (PDMA) a part of the FDCA.

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In the United States, once a product is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These manufacturers must comply with cGMP regulations that require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. The discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including, among other things, recall or withdrawal of the product from the market.

Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Other Regulatory Matters

Manufacturing, sales, promotion and other activities following product approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the U.S., the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the U.S. Department of Justice, the Drug Enforcement Administration, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments. In the U.S., sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. These laws include the federal Anti-Kickback Statute, which makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration that is intended to induce the referral of business, including the purchase, order, or prescription of a particular drug, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties, and exclusion from participation in federal healthcare programs. In addition, the Patient Protection and Affordable Health Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the ACA, among other things, amends the intent requirement of the federal Anti-Kickback Statute and criminal healthcare fraud statutes created by the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. Moreover, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal anti-kickback statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Although we would not submit claims directly to payors, drug manufacturers can be held liable under the federal False Claims Act, which prohibits anyone from knowingly presenting, or causing to be presented, for payment to federal programs (including Medicare and Medicaid) claims for items or services, including drugs, that are false or fraudulent, claims for items or services not provided as claimed, or claims for medically unnecessary items or services. The government may deem manufacturers to have “caused” the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers or promoting a product off-label. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products, are subject to scrutiny under this law. Penalties for a False Claims Act violation include three times the actual damages sustained by the government, plus mandatory civil penalties of between \$5,500 and \$11,000 for each separate false claim, the potential for exclusion from participation in federal healthcare programs, and, although the federal False Claims Act is a civil statute, conduct that results in a False Claims Act violation may also implicate various federal criminal statutes. If the government were to allege that we were, or convict us of, violating these false claims laws, we could be subject to a substantial fine and may suffer a decline in our stock price. In addition, private individuals have the ability to bring actions under the federal False Claims Act and certain states have enacted laws modeled after the federal False Claims Act.

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Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in ACA. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The failure to comply with any of these laws or regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the U.S. Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application (ANDA) or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator

drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the non-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

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European Union Drug Development

In the European Union (EU), our future products may also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if a marketing authorization from the competent regulatory agencies has been obtained.

Similar to the U.S., the various phases of non-clinical and clinical research in the European Union are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the EU countries where the trial is to be conducted by two distinct bodies: the National Competent Authority (NCA) and one or more Ethics Committees (ECs). Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred.

The EU clinical trials legislation is currently undergoing a revision process mainly aimed at harmonizing and streamlining the clinical trials authorization process, simplifying adverse event reporting procedures, improving the supervision of clinical trials, and increasing their transparency.

European Union Drug Review and Approval

In the European Economic Area (EEA) (which is comprised of the 27 Member States of the European Union (excluding Croatia) plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, (MA). There are two types of marketing authorizations:

The Community MA is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State (RMS). The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics (SPC) and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the Member States Concerned).

Under the above-described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

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European Union New Chemical Entity Exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

European Union Orphan Designation and Exclusivity

In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the European Union Community and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the medicinal product.

In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Rest of the World Regulation

For other countries outside of the EU and the U.S., such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with cGCP requirements and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. In the United States no uniform policy of coverage and reimbursement for drug products exists. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will be made on a payor by payor basis. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be obtained.

Third-party payors are increasingly reducing reimbursements for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our product candidate or a decision by a third-party payor to not cover our product candidate could reduce physician usage of the product candidate and have a material adverse effect on our sales, results of operations and financial condition.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the MMA) established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

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The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by the U.S. Department of Health and Human Services, the Agency for Healthcare Research and Quality and the NIH, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our product candidate, if any such product or the condition that it is intended to treat is the subject of a trial. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidate. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The ACA is expected to have a significant impact on the health care industry. The ACA is expected to expand coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, among other things, the ACA is expected to expand and increase industry rebates for drugs covered under Medicaid programs and make changes to the coverage requirements under the Medicare Part D program. We cannot predict the full impact of the ACA on our business as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions that has not yet occurred. For example, the ACA imposed new reporting requirements on drug manufacturers for payments made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. Failure to submit required information may result in civil monetary penalties of up to an aggregate of \$150,000 per year (or up to an aggregate of \$1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests that are not timely, accurately and completely reported in an annual submission. Drug manufacturers were required to begin collecting data on August 1, 2013 and were required to submit reports to CMS by March 31, 2014 (and by the 90th day of each subsequent calendar year). In addition, many states have adopted laws similar to the federal laws discussed above. Some of these state prohibitions apply to the referral of patients for healthcare services reimbursed by any insurer, not just federal healthcare programs such as Medicare and Medicaid. There has also been a recent trend of increased federal and state regulation of payments made to physicians. Certain states mandate implementation of compliance programs, impose restrictions on drug manufacturers' marketing practices and/or require the tracking and reporting of gifts, compensation and other remuneration to physicians. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, started in April 2013. On January 2, 2013, President Obama signed into law the American Taxpayer Relief Act of 2012 (the ATRA), which delayed for another two months the budget cuts mandated by these sequestration provisions of the Budget Control Act of 2011. The ATRA, among other things, also reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect

controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the U.S. and generally prices tend to be significantly lower.

Stem Cell Technology - United States

With respect to our stem cell research and development in the U.S., the U.S. government has established requirements and procedures relating to the isolation and derivation of certain stem cell lines and the availability of federal funds for research and development programs involving those lines. All of the stem cell lines that we are using were either isolated under procedures that meet U.S. government requirements and are approved for funding from the U.S. government, or were isolated under procedures that meet U.S. government requirements.

All procedures we use to obtain clinical samples, and the procedures we use to isolate hESCs, are consistent with the informed consent and ethical guidelines promulgated by the U.S. National Academy of Science, the International Society of Stem Cell Research (ISSCR), or the NIH. These procedures and documentation have been reviewed by an external Stem Cell Research Oversight Committee, and all cell lines we use have been approved under one or more of these guidelines.

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The U.S. government and its agencies on July 7, 2009 published guidelines for the ethical derivation of hESCs required for receiving federal funding for hESC research. Should we seek further NIH funding for our stem cell research and development, our request would involve the use of hESC lines that meet the NIH guidelines for NIH funding. In the U.S., the President's Council on Bioethics monitors stem cell research, and may make recommendations from time to time that could place restrictions on the scope of research using human embryonic or fetal tissue. Although numerous states in the U.S. are considering, or have in place, legislation relating to stem cell research, including California whose voters approved Proposition 71 to provide up to \$3 billion of state funding for stem cell research in California, it is not yet clear what affect, if any, state actions may have on our ability to commercialize stem cell technologies.

Stem Cell Technology - Canada

In Canada, stem cell research and development is governed by two policy documents and by one legislative statute: the Guidelines for Human Pluripotent Stem Cell Research (the Guidelines) issued by the Canadian Institutes of Health Research; the Tri-Council Statement: Ethical Conduct for Research Involving Humans (TCPS); and the Assisted Human Reproduction Act (Act). The Guidelines and the TCPS govern stem cell research conducted by, or under the auspices of, institutions funded by the federal government. Should we seek funding from Canadian government agencies or should we conduct research under the auspices of an institution so funded, we may have to ensure the compliance of such research with the ethical rules prescribed by the Guidelines and the TCPS.

The Act subjects all research conducted in Canada involving the human embryo, including hESC derivation (but not the stem cells once derived), to a licensing process overseen by a federal licensing agency. However, as of the date of this Annual Report, the provisions of the Act regarding the licensing of hESC derivation were not in force.

We are not currently conducting stem cell research in Canada. We have, however, sponsored pluripotent stem cell research in Canada by Dr. Gordon Keller at UHN's McEwen Centre. We anticipate conducting additional hPSC research (with both hESCs and hiPSCs), in collaboration with Dr. Keller and his research team, at UHN's McEwen Centre during 2015 and beyond. Should the provisions of the Act come into force, we may have to apply for a license for all hESC research we may sponsor or conduct in Canada and ensure compliance of such research with the provisions of the Act.

Subsidiaries and Inter-Corporate Relationships

VistaGen Therapeutics, Inc., a California corporation, is our wholly-owned subsidiary and has the following two wholly-owned subsidiaries: VistaStem Canada Inc., a corporation incorporated pursuant to the laws of the Province of Ontario, intended to facilitate our stem cell-based research and development and drug rescue activities in Canada should we elect to expand our U.S. operations into Canada; and Artemis Neuroscience, Inc., a corporation incorporated pursuant to the laws of the State of Maryland. The operations of VistaGen Therapeutics, Inc., a California corporation, and each of its two wholly owned subsidiaries are managed by our senior management team based in South San Francisco, California.

Employees

As of June 24, 2016, we employed nine full-time employees, four of whom have doctorate degrees. Six full-time employees work in research and development and laboratory support services and three full-time employees work in general and administrative roles. Staffing for all other functional areas is achieved through strategic relationships with service providers and consultants, each of whom provides services on a real-time, as-needed basis, including human resources and payroll, information technology, facilities, legal, stock plan administration, investor relations and website maintenance, regulatory affairs, and FDA program management.

We have never had a work stoppage, and none of our employees is represented by a labor organization or under any collective bargaining agreement. We consider our employee relations to be good.

Facilities

We lease our office and laboratory space, which consists of approximately 10,000 square feet located in South San Francisco, California. Our lease expires on July 31, 2017. We intend to renew the lease at our current location in the ordinary course of business, prior to the end of July 2017.

Legal Proceedings

None.

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Environmental Regulation

Our business does not require us to comply with any particular unique environmental regulations.

Item 1A. Risk Factors

Investing in our securities involves a high degree of risk. You should consider carefully the risks and uncertainties described below, together with all of the other information in this Annual Report before investing in our securities. The risks described below are not the only risks facing our Company. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial may also materially adversely affect our business, financial condition and/or operating results. If any of the following risks are realized, our business, financial condition and results of operations could be materially and adversely affected.

Risks Related to Product Development, Regulatory Approval and Commercialization

We depend heavily on the success of AV-101. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize AV-101, or any product candidate.

We currently have no drug products for sale and may never be able to develop and commercialize marketable drug products. Our business depends heavily on the successful development, regulatory approval and commercialization of AV-101 for depression, including for MDD, and various other diseases and disorders involving the CNS, as well as, but to a more limited extent, our ability to produce, develop and commercialize NCEs from our drug rescue programs. AV-101 will require substantial additional Phase 2 and Phase 3 clinical development, testing and regulatory approval before we are permitted to commence its commercialization and is unlikely to achieve regulatory approval until at least 2021, if at all. Each drug rescue NCE will require substantial non-clinical development, all phases of clinical development, and regulatory approval before we are permitted to commence its commercialization. The non-clinical studies and clinical trials of our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market any product candidate. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through non-clinical studies and clinical trials that the product candidate is safe and effective for use in each target indication. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our non-clinical studies or clinical trials. This process can take many years and may also include post-marketing studies and surveillance, which will require the expenditure of substantial resources beyond the proceeds we have raised to date. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our non-clinical studies and clinical trials, we cannot assure you that AV-101, any drug rescue NCE, or any other product candidate will be successfully developed or commercialized.

We are not permitted to market our product candidates in the United States until we receive approval of a New Drug Application (NDA) from the FDA, or in any foreign countries until we receive the requisite approval from such countries. In late 2015, in collaboration with the NIMH under our CRADA, we began a Phase 2a clinical trial involving AV-101, to study its safety, tolerability and efficacy in patients with MDD. If our Phase 2a clinical trial of AV-101 is successful, we expect the FDA to require us to complete at least one pivotal Phase 2B clinical trial and at least one pivotal Phase 3 clinical trial in order to submit an NDA for AV-101 as an adjunctive treatment for MDD. However, the FDA may require that we conduct more than one Phase 2B clinical study and more than one Phase 3 pivotal trial of AV-101 before we can submit an NDA. Also, we anticipate that the FDA will require that we conduct additional toxicity studies and additional non-clinical studies before submitting an NDA for AV-101.

Obtaining FDA approval of an NDA is a complex, lengthy, expensive and uncertain process, and the FDA may delay, limit or deny approval of AV-101 or any of our product candidates for many reasons, including, among others:

if our NDA, if and when submitted, is reviewed by an advisory committee, the FDA may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee may recommend against approval of our application or may recommend that the FDA require, as a condition of approval, additional non-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;

the FDA may require development of a Risk Evaluation and Mitigation Strategy (REMS) as a condition of approval or post-approval;

the FDA or the applicable foreign regulatory agency may determine that the manufacturing processes or facilities of third-party contract manufacturers with which we contract do not conform to applicable requirements, including current Good Manufacturing Practices (cGMPs); or

the FDA or applicable foreign regulatory agency may change its approval policies or adopt new regulations.

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Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully commercialize AV-101 or any other product candidate we may develop, including drug rescue NCEs. Any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

We intend to seek a Fast Track designation from the FDA for AV-101 for treatment of MDD. Even if the FDA approves Fast Track designation for AV-101 for treatment of MDD, it may not actually lead to a faster development or regulatory review or approval process.

The Fast Track designation is a program offered by the FDA pursuant to certain mandates under the FDA Modernization Act of 1997, designed to facilitate drug development and to expedite the review of new drugs that are intended to treat serious or life threatening conditions. Compounds selected must demonstrate the potential to address unmet medical needs. The Fast Track designation allows for close and frequent interaction with the FDA. A designated Fast Track drug may also be considered for priority review with a shortened review time, rolling submission, and accelerated approval if applicable. The designation does not, however, guarantee approval or expedited approval of any application for the product.

We intend to seek FDA Fast Track designation for AV-101 for adjunctive treatment of MDD, and we may do so for other product candidates as well. The FDA has broad discretion whether or not to grant this designation, and even if we believe AV-101 and other product candidates are eligible for this designation, we cannot be sure that the review or approval will compare to conventional FDA procedures. Even if granted, the FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development programs.

The number of patients suffering from MDD has not been established with precision. If the actual number of patients with MDD is smaller than we anticipate, we or our collaborators may encounter difficulties in enrolling patients in AV-101 clinical trials, including our NIH-funded Phase 2a clinical study of AV-101 in MDD, thereby delaying or preventing clinical development. Further, if AV-101 is approved for adjunctive treatment of MDD, and the market for this indication is smaller than we anticipate, our ability to achieve profitability could be limited.

Results of earlier clinical trials may not be predictive of the results of later-stage clinical trials.

The results of preclinical studies and early clinical trials of AV-101 and other product candidates may not be predictive of the results of later-stage clinical trials. AV-101 or other product candidates in later stages of clinical trials may fail to show the desired safety and efficacy results despite having progressed through preclinical studies and initial clinical trials. Many companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to adverse safety profiles or lack of efficacy, notwithstanding promising results in earlier studies. Similarly, our future clinical trial results may not be successful for these or other reasons.

This drug candidate development risk is heightened by any changes in planned clinical trials compared to completed clinical trials. As product candidates are developed through preclinical to early and late stage clinical trials towards approval and commercialization, it is customary that various aspects of the development program, such as manufacturing and methods of administration, are altered along the way in an effort to optimize processes and results. While these types of changes are common and are intended to optimize the product candidates for later stage clinical trials, approval and commercialization, such changes do carry the risk that they will not achieve these intended objectives.

For example, the results of planned clinical trials may be adversely affected if we or our collaborator seek to optimize and scale-up production of a product candidate. In such case, we will need to demonstrate comparability between the newly manufactured drug substance and/or drug product relative to the previously manufactured drug substance

and/or drug product. Demonstrating comparability may cause us to incur additional costs or delay initiation or completion of our clinical trials, including the need to initiate a dose escalation study and, if unsuccessful, could require us to complete additional preclinical or clinical studies of our product candidates.

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If serious adverse events or other undesirable side effects are identified during the use of AV-101 in clinical trials, it may adversely effect our development of AV-101 for MDD and other CNS indications.

AV-101 is currently being tested in an NIH-investigator sponsored Phase 2a clinical trial for the treatment of MDD and may be subjected to testing in the future for other CNS indications in additional investigator sponsored clinical trials. If serious adverse events or other undesirable side effects, or unexpected characteristics of AV-101 are observed in investigator sponsored clinical trials of AV-101 or our clinical trials, it may adversely affect or delay our clinical development of AV-101, and the occurrence of these events would have a material adverse effect on our business.

Positive results from early preclinical studies and clinical trials of AV-101 or other product candidates are not necessarily predictive of the results of later preclinical studies and clinical trials of such product candidates. If we cannot replicate the positive results from our earlier preclinical studies and clinical trials of AV-101 or other product candidates in our later preclinical studies and clinical trials, we may be unable to successfully develop, obtain regulatory approval for and commercialize our product candidates.

Positive results from preclinical studies of our product candidates, and any positive results we may obtain from early clinical trials of our product candidates, may not necessarily be predictive of the results from required later preclinical studies and clinical trials. Similarly, even if we are able to complete our planned preclinical studies or clinical trials of our product candidates according to our current development timeline, the positive results from our preclinical studies and clinical trials of our product candidates may not be replicated in subsequent preclinical studies or clinical trial results. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in early-stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, preclinical findings made while clinical trials were underway or safety or efficacy observations made in preclinical studies and clinical trials, including previously unreported adverse events. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA approval. We have not yet completed a Phase 2a clinical trial for AV-101, and if we fail to produce positive results in our NIH-sponsored Phase 2a clinical trial of AV-101 in MDD, the development timeline and regulatory approval and commercialization prospects for AV-101 and, correspondingly, our business and financial prospects, could be materially adversely affected.

Failures or delays in the commencement or completion of our planned clinical trials of our product candidates could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

Under our CRADA, we and the NIH have commenced an NIH-funded Phase 2a clinical trial of AV-101 as a treatment for MDD. We will need to complete at least two additional large clinical trials prior to the submission of an NDA for AV-101 as a treatment for MDD. Successful completion of our clinical trials is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of AV-101 for MDD and any other product candidates we may develop. We do not know whether the NIH-funded Phase 2a study of AV-101 or any of our future-planned clinical trials will be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- the FDA may deny permission to proceed with our planned clinical trials or any other clinical trials we may initiate, or may place a clinical trial on hold;

- delays in filing or receiving approvals of additional INDs that may be required;

negative results from our ongoing pre-clinical studies;

delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical trials, for example delays in the manufacturing of sufficient supply of finished drug product;

difficulties obtaining Institutional Review Board (IRB) approval to conduct a clinical trial at a prospective site or sites;

challenges in recruiting and enrolling patients to participate in clinical trials, including the proximity of patients to trial sites;

eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;

severe or unexpected drug-related side effects experienced by patients in a clinical trial;

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delays in validating any endpoints utilized in a clinical trial;

the FDA may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials;

reports from pre-clinical or clinical testing of other CNS therapies that raise safety or efficacy concerns; and

difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trials, lack of efficacy, side effects, personal issues or loss of interest.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, the FDA, the IRBs at the sites where the IRBs are overseeing a clinical trial, a data and safety monitoring board (DSMB), overseeing the clinical trial at issue or other regulatory authorities due to a number of factors, including, among others:

failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;

inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;

unforeseen safety issues, including any that could be identified in our ongoing non-clinical carcinogenicity studies, adverse side effects or lack of effectiveness;

changes in government regulations or administrative actions;

problems with clinical supply materials; and

lack of adequate funding to continue clinical trials.

Changes in regulatory requirements, FDA guidance or unanticipated events during our preclinical studies and clinical trials of our product candidates may occur, which may result in changes to preclinical studies and clinical trial protocols or additional preclinical studies and clinical trial requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance or unanticipated events during our preclinical studies and clinical trials may force us to amend preclinical studies and clinical trial protocols or the FDA may impose additional preclinical studies and clinical trial requirements. Amendments or changes to our clinical trial protocols would require resubmission to the FDA and IRBs for review and approval, which may adversely impact the cost, timing or successful completion of clinical trials. Similarly, amendments to our pre-clinical studies may adversely impact the cost, timing, or successful completion of those pre-clinical studies. If we experience delays completing, or if we terminate, any of our pre-clinical studies or clinical trials, or if we are required to conduct additional pre-clinical studies or clinical trials, the commercial prospects for our product candidates may be harmed and our ability to generate product revenue will be delayed.

We rely, and expect that we will continue to rely, on third parties to conduct any clinical trials for our product candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We do not have the ability to independently conduct clinical trials. We rely on medical institutions, clinical investigators, contract laboratories and other third parties, such as CROs, to conduct clinical trials on our product candidates. We enter into agreements with third-party CROs to provide monitors for and to manage data for our clinical trials. We rely heavily on these parties for execution of clinical trials for our product candidates and control only certain aspects of their activities. As a result, we have less direct control over the conduct, timing and completion of these clinical trials and the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

have staffing difficulties;

fail to comply with contractual obligations;

experience regulatory compliance issues;

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undergo changes in priorities or become financially distressed; or
form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific requirements and standards, and our reliance on CROs or the NIH does not relieve us of our regulatory responsibilities. We and our CROs and the NIMH are required to comply with regulations and guidelines, including current cGCPs for conducting, monitoring, recording and reporting the results of clinical trials to ensure that the data and results are scientifically credible and accurate, and that the trial patients are adequately informed of the potential risks of participating in clinical trials. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any products in clinical development. The FDA enforces cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical trials comply with cGCPs. In addition, our clinical trials must be conducted with product candidates produced under cGMPs regulations and will require a large number of test patients. Our failure or the failure of our CROs to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action up to and including civil and criminal penalties.

Although we design our clinical trials for our product candidates, we plan to have CROs, and in the case of our initial AV-101 Phase 2a study in MDD, the NIH, conduct the AV-101 Phase 2 and Phase 3 clinical trials. As a result, many important aspects of our drug development programs are outside of our direct control. In addition, the CROs or the NIH, as the case may be, may not perform all of their obligations under arrangements with us or in compliance with regulatory requirements, but we remain responsible and are subject to enforcement action that may include civil penalties up to and including criminal prosecution for any violations of FDA laws and regulations during the conduct of our clinical trials. If the NIH or CROs do not perform clinical trials in a satisfactory manner, breach their obligations to us or fail to comply with regulatory requirements, the development and commercialization of AV-101 and other product candidates may be delayed or our development program materially and irreversibly harmed. We cannot control the amount and timing of resources these CROs or the NIH devote to our program or our clinical products. If we are unable to rely on clinical data collected by our CROs or the NIH, we could be required to repeat, extend the duration of, or increase the size of our clinical trials and this could significantly delay commercialization and require significantly greater expenditures.

If any of our relationships with these third-party CROs or the NIH terminate, we may not be able to enter into arrangements with alternative CROs or collaborators. If CROs or the NIH do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any clinical trials that such CROs or the NIH are associated with may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, we believe that our financial results and the commercial prospects for our product candidates in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

We rely completely on third-party suppliers to manufacture our clinical drug supplies for our product candidates, and we intend to rely on third parties to produce non-clinical, clinical and commercial supplies of any future product

candidate.

We do not currently have, nor do we plan to acquire, the infrastructure or capability to internally manufacture our clinical drug supply of AV-101 or any other product candidates for use in the conduct of our nonclinical studies and clinical trials, and we lack the internal resources and the capability to manufacture any product candidates on a clinical or commercial scale. The facilities used by our contract manufacturers to manufacture the active pharmaceutical ingredient and final drug product must complete a pre-approval inspection by the FDA and other comparable foreign regulatory agencies to assess compliance with applicable requirements, including cGMPs, after we submit our NDA or relevant foreign regulatory submission to the applicable regulatory agency.

We do not control the manufacturing process of, and are completely dependent on, our contract manufacturers to comply with cGMPs for manufacture of both active drug substances and finished drug products. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or applicable foreign regulatory agencies, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no direct control over our contract manufacturers' ability to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, all of our contract manufacturers are engaged with other companies to supply and/or manufacture materials or products for such companies, which exposes our third-party contract manufacturers to regulatory risks for the production of such materials and products. As a result, failure to satisfy the regulatory requirements for the production of those materials and products may affect the regulatory clearance of our contract manufacturers' facilities generally. If the FDA or an applicable foreign regulatory agency determines now or in the future that these facilities for the manufacture of our product candidates are noncompliant, we may need to find alternative manufacturing facilities, which would adversely impact our ability to develop, obtain regulatory approval for or market our product candidates. Our reliance on contract manufacturers also exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may appropriate our trade secrets or other proprietary information.

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We do not have long-term supply agreements in place with our contract manufacturers and each batch of our product candidates are individually contracted under a quality and supply agreement. If we engage new contract manufacturers, such contractors must complete an inspection by the FDA and other applicable foreign regulatory agencies. We plan to continue to rely upon contract manufacturers and, potentially, collaboration partners, to manufacture commercial quantities of AV-101 and other product candidates, if approved. Our current scale of manufacturing for AV-101 is adequate to support our currently planned needs for additional pre-clinical studies and clinical trial supplies.

Even if we receive marketing approval for our product candidates in the United States, we may never receive regulatory approval to market our product candidates outside of the United States.

We have not yet selected any markets outside of the United States where we intend to seek regulatory approval to market our product candidates. In order to market any product outside of the United States, however, we must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of other countries. Approval procedures vary among countries and can involve additional product candidate testing and additional administrative review periods. The time required to obtain approvals in other countries might differ from that required to obtain FDA approval. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States as well as other risks. In particular, in many countries outside of the United States, products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval can result in substantial delays in bringing products to market in such countries. Marketing approval in one country does not ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process in others. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair our ability to market our product candidates in such foreign markets. Any such impairment would reduce the size of our potential market, which could have a material adverse impact on our business, results of operations and prospects.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may not be able to generate any revenue.

We do not currently have an infrastructure for the sales, marketing and distribution of pharmaceutical products, nor do we intend to create such capabilities. Therefore, in order to market our product candidates globally, if approved by the FDA or any other regulatory body, we must make contractual arrangements with third parties to perform services related to sales, marketing, managerial and other non-technical capabilities relating to the commercialization of our product candidates. If we are unable to establish adequate contractual arrangements for such sales, marketing and distribution capabilities, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition and prospects will be materially adversely affected.

Even if we receive marketing approval for our product candidates, our product candidates may not achieve broad market acceptance, which would limit the revenue that we generate from their sales.

The commercial success of our product candidates, if approved by the FDA or other applicable regulatory authorities, will depend upon the awareness and acceptance of our product candidates among the medical community, including physicians, patients and healthcare payors. Market acceptance of our product candidates, if approved, will depend on a number of factors, including, among others:

the efficacy of our product candidates as demonstrated in clinical trials, and, if required by any applicable regulatory authority in connection with the approval for the applicable indications, to provide patients with incremental health benefits, as compared with other available therapies;

limitations or warnings contained in the labeling approved for our product candidates by the FDA or other applicable regulatory authorities;

the clinical indications for which our product candidates are approved;

availability of alternative treatments already approved or expected to be commercially launched in the near future;

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the potential and perceived advantages of our product candidates over current treatment options or alternative treatments, including future alternative treatments;

the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;

the strength of marketing and distribution support and timing of market introduction of competitive products;

publicity concerning our products or competing products and treatments;

pricing and cost effectiveness;

the effectiveness of our sales and marketing strategies;

our ability to increase awareness of our product candidates through marketing efforts;

our ability to obtain sufficient third-party coverage or reimbursement; or

the willingness of patients to pay out-of-pocket in the absence of third-party coverage.

If our product candidates are approved but do not achieve an adequate level of acceptance by patients, physicians and payors, we may not generate sufficient revenue from our product candidates to become or remain profitable. Before granting reimbursement approval, healthcare payors may require us to demonstrate that our product candidates, in addition to treating these target indications, also provide incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of our product candidates may require significant resources and may never be successful.

Our product candidates may cause undesirable side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt nonclinical studies and clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other regulatory authorities.

Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product candidate. If our product candidates receive marketing approval and we or others identify undesirable side effects caused by such product candidates (or any other similar products) after such approval, a number of potentially significant negative consequences could result, including:

regulatory authorities may withdraw or limit their approval of such product candidates;

regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;

we may be required to change the way such product candidates are distributed or administered, conduct additional clinical trials or change the labeling of the product candidates;

we may be subject to regulatory investigations and government enforcement actions;

we may decide to remove such product candidates from the marketplace;

we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and

our reputation may suffer.

We believe that any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidates and could substantially increase the costs of commercializing our product candidates and significantly impact our ability to successfully commercialize our product candidates and generate revenues.

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Even if we receive marketing approval for our product candidates, we may still face future development and regulatory difficulties.

Even if we receive marketing approval for our product candidates, regulatory authorities may still impose significant restrictions on our product candidates, indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. Our product candidates will also be subject to ongoing FDA requirements governing the labeling, packaging, storage and promotion of the product and record keeping and submission of safety and other post-market information. The FDA has significant post-marketing authority, including, for example, the authority to require labeling changes based on new safety information and to require post-marketing studies or clinical trials to evaluate serious safety risks related to the use of a drug. The FDA also has the authority to require, as part of an NDA or post-approval, the submission of a REMS. Any REMS required by the FDA may lead to increased costs to assure compliance with new post-approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue.

Manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMPs and other regulations. If we or a regulatory agency discover problems with our product candidates, such as adverse events of unanticipated severity or frequency, or problems with the facility where our product candidates are manufactured, a regulatory agency may impose restrictions on our product candidates, the manufacturer or us, including requiring withdrawal of our product candidates from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

issue warning letters or untitled letters;

seek an injunction or impose civil or criminal penalties or monetary fines;

suspend or withdraw marketing approval;

suspend any ongoing clinical trials;

refuse to approve pending applications or supplements to applications submitted by us;

suspend or impose restrictions on operations, including costly new manufacturing requirements; or

seize or detain products, refuse to permit the import or export of products, or require that we initiate a product recall.

Competing therapies could emerge adversely affecting our opportunity to generate revenue from the sale of our product candidates.

The pharmaceuticals industry is highly competitive. There are many public and private pharmaceutical companies, universities, governmental agencies and other research organizations actively engaged in the research and development of products that may be similar to our product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products will increase.

Currently, management is unaware of any FDA-approved adjunctive therapy for treatment-resistant MDD with the same mechanism of action and safety profile as AV-101. However, new antidepressant products with other mechanisms of action or products approved for other indications, including the anesthetic ketamine, are being or may be used off-label for treatment of MDD, as well as other CNS indications for which AV-101 may have therapeutic

potential. Additionally, other non-pharmaceutical treatment options, such as psychotherapy and electroconvulsive therapy (ECT) are sometimes used before or instead of standard antidepressants to treat patients with MDD.

In the field of new generation antidepressants focused on modulation of the NMDA receptor at the glycine binding co-agonist site, we believe our principal competitor is Allergan, which recently acquired from and is now developing both the intravenously-administered peptide, rapastinel (formerly GLYX-13), and NRX-1074, which may be or may become orally-available, for treatment-resistant MDD.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. We believe that a range of pharmaceutical and biotechnology companies have programs to develop small molecule drug candidates for the treatment of depression, including MDD, epilepsy, neuropathic pain, Parkinson's disease and other neurological conditions and diseases, including, but not limited to, Abbott Laboratories, Acadia, Allergan, Alkermes, Astra Zeneca, Eli Lilly, GlaxoSmithKline, IntraCellular, Johnson & Johnson, Lundbeck, Merck, Novartis, Ono, Otsuka, Pfizer, Roche, Sumitomo Dainippon, Teva and Takeda. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

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We may seek to establish collaborations, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate. The terms of any collaboration or other arrangements that we may establish may not be favorable to us.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

In addition, any future collaboration that we enter into may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority. Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

We may not be successful in our efforts to identify or discover additional product candidates or we may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

The success of our business depends primarily upon our ability to identify, develop and commercialize product candidates with commercial and therapeutic potential. Although AV-101 is in Phase 2 clinical development for treatment of depression, we may fail to pursue additional CNS-related Phase 2 development opportunities for AV-101, or identify additional product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying new product candidates or our product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

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Because we have limited financial and management resources, we focus on a limited number of research programs and product candidates and are currently focused primarily on development of AV-101, with additional limited focus on NCE drug rescue and RM. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other potential CNS-related indications for AV-101 that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable drugs. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through future collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

We are subject to healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Although we do not currently have any products on the market, once we begin commercializing our products, we may be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. Healthcare providers, physicians and others will play a primary role in the recommendation and prescription of our product candidates, if approved. Our future arrangements with third-party payors will expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our product candidates, if we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

The federal anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid.

The federal False Claims Act imposes criminal and civil penalties, including those from civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government.

The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.

The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.

The federal transparency requirements, sometimes referred to as the “Sunshine Act,” under the Patient Protection and Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable

under Medicare, Medicaid, or the Children's Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests.

Analogous state laws and regulations, such as state anti-kickback and false claims laws and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance.

Guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and drug pricing.

Ensuring that our future business arrangements with third parties comply with applicable healthcare laws and regulations could be costly. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities to be conducted by our sales team, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines and exclusion from government funded healthcare programs, such as Medicare and Medicaid, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. If we are found to have improperly promoted off-label uses, we may become subject to significant liability.

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, such as AV-101, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. For example, if we receive marketing approval for AV-101 as an augmentation therapy for MDD, physicians may nevertheless prescribe AV-101 to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Even if approved, reimbursement policies could limit our ability to sell our product candidates.

Market acceptance and sales of our product candidates will depend on reimbursement policies and may be affected by healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels for those medications. Cost containment is a primary concern in the U.S. healthcare industry and elsewhere. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that reimbursement will be available for our product candidates and, if reimbursement is available, the level of such reimbursement. Reimbursement may impact the demand for, or the price of, our product candidates. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates.

In some foreign countries, particularly in Canada and European countries, the pricing of prescription pharmaceuticals is subject to strict governmental control. In these countries, pricing negotiations with governmental authorities can take six months or longer after the receipt of regulatory approval and product launch. To obtain favorable reimbursement for the indications sought or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates with other available therapies. If reimbursement for our product candidates is unavailable in any country in which we seek reimbursement, if it is limited in scope or amount, if it is conditioned upon our completion of additional clinical trials, or if pricing is set at unsatisfactory levels, our operating results could be materially adversely affected.

Even if we have obtained FDA Orphan Drug designation for one or more of our product candidates, there may be limits to the regulatory exclusivity afforded by such designation.

Even if we obtain Orphan Drug designation from the FDA for one or more of our product candidates, there are limitations to exclusivity afforded by such designation. In the United States, the company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years. This orphan drug exclusivity prevents the FDA from approving another application, including a full NDA to market the same drug for the same orphan indication, except in very limited circumstances, including when the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. For purposes of small molecule drugs, the FDA defines "same drug" as a drug that contains the same active moiety and is intended for the same use as the drug in question. To obtain orphan drug exclusivity for a drug that shares the same active moiety as an already approved drug, it must be demonstrated to the FDA that the

drug is safer or more effective than the approved orphan designated drug, or that it makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition or if another drug with the same active moiety is determined to be safer, more effective, or represents a major contribution to patient care.

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Our future growth may depend, in part, on our ability to penetrate foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future profitability may depend, in part, on our ability to commercialize our product candidates in foreign markets for which we may rely on collaboration with third parties. If we commercialize our product candidates in foreign markets, we would be subject to additional risks and uncertainties, including:

our customers' ability to obtain reimbursement for our product candidates in foreign markets;

our inability to directly control commercial activities because we are relying on third parties;

the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;

different medical practices and customs in foreign countries affecting acceptance in the marketplace;

import or export licensing requirements;

longer accounts receivable collection times;

longer lead times for shipping;

language barriers for technical training;

reduced protection of intellectual property rights in some foreign countries;

the existence of additional potentially relevant third party intellectual property rights;

foreign currency exchange rate fluctuations; and

the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of our product candidates could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

We are a development stage biopharmaceutical company with no current revenues or approved products, and limited experience developing new drug, biological and/or regenerative medicine candidates, including conducting clinical trials and other areas required for the successful development and commercialization of therapeutic products, which makes it difficult to assess our future viability.

We are a development stage biopharmaceutical company. Although our lead drug candidate is in Phase 2 development, we currently have no approved products and currently generate no revenues, and we have not yet fully demonstrated an ability to overcome many of the fundamental risks and uncertainties frequently encountered by development stage companies in new and rapidly evolving fields of technology, particularly biotechnology. To execute our business plan successfully, we will need to accomplish the following fundamental objectives, either on our own or with strategic collaborators:

produce product candidates;

develop and obtain required regulatory approvals for commercialization of products we produce;

maintain, leverage and expand our intellectual property portfolio;

establish and maintain sales, distribution and marketing capabilities, and/or enter into strategic partnering arrangements to access such capabilities;

gain market acceptance for our products; and

obtain adequate capital resources and manage our spending as costs and expenses increase due to research, production, development, regulatory approval and commercialization of product candidates.

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Our future success is highly dependent upon our ability to successfully develop and commercialize AV-101 and discover, as well as produce, develop and commercialize proprietary drug rescue NCEs using our stem cell technology, and we cannot provide any assurance that we will successfully develop and commercialize AV-101 or drug rescue NCEs, or that, if produced, AV-101 or any drug rescue NCE will be successfully commercialized.

Research programs designed to identify and produce drug rescue NCEs require substantial technical, financial and human resources, whether or not any NCEs are ultimately identified and produced. In particular, our drug rescue programs may initially show promise in identifying potential NCEs, yet fail to yield a lead NCE suitable for preclinical, clinical development or commercialization for many reasons, including the following:

our drug rescue research methodology may not be successful in identifying potential drug rescue NCEs;

competitors may develop alternatives that render our drug rescue NCEs obsolete;

a drug rescue NCE may, on further study, be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;

a drug rescue NCE may not be capable of being produced in commercial quantities at an acceptable cost, or at all; or

a drug rescue NCE may not be accepted as safe and effective by regulatory authorities, patients, the medical community or third-party payors.

In addition, we do not have a sales or marketing infrastructure, and we, including our executive officers, do not have any significant pharmaceutical sales, marketing or distribution experience. We may seek to collaborate with others to develop and commercialize AV-101, drug rescue NCEs and/or other product candidates if and when they are developed. If we enter into arrangements with third parties to perform sales, marketing and distribution services for our products, the resulting revenues or the profitability from these revenues to us are likely to be lower than if we had sold, marketed and distributed our products ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute AV-101, any drug rescue NCEs or other product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of these third parties may fail to devote the necessary resources and attention to sell, market and distribute our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, in collaboration with third parties, we will not be successful in commercializing our product candidates.

We have limited operating history with respect to drug development, including our anticipated focus on the identification and assessment of potential drug rescue NCEs and no operating history with respect to the production of drug rescue NCEs, and we may never be able to produce a drug rescue NCE.

If we are unable to develop and commercialize AV-101 or produce suitable drug rescue NCEs, we may not be able to generate sufficient revenues to execute our business plan, which likely would result in significant harm to our financial position and results of operations, which could adversely impact our stock price.

There are a number of factors, in addition to the utility of CardioSafe 3D, that may impact our ability to identify and produce, develop or out-license and commercialize drug rescue NCEs, independently or with strategic partners, including:

our ability to identify potential drug rescue candidates in the public domain, obtain sufficient quantities of them, and assess them using our bioassay systems;

if we seek to rescue drug rescue candidates that are not available to us in the public domain, the extent to which third parties may be willing to out-license or sell certain drug rescue candidates to us on commercially reasonable terms;

our medicinal chemistry collaborator's ability to design and produce proprietary drug rescue NCEs based on the novel biology and structure-function insight we provide using CardioSafe 3D; and

financial resources available to us to develop and commercialize lead drug rescue NCEs internally, or, if we out-license them to strategic partners, the resources such partners choose to dedicate to development and commercialization of any drug rescue NCEs they license from us.

Even if we do produce proprietary drug rescue NCEs, we can give no assurance that we will be able to develop and commercialize them as a marketable drug, on our own or in collaboration with others. Before we generate any revenues from AV-101 and/or additional drug rescue NCEs we or our potential collaborators must complete preclinical and clinical developments, submit clinical and manufacturing data to the FDA, qualify a third party contract manufacturer, receive regulatory approval in one or more jurisdictions, satisfy the FDA that our contract manufacturer is capable of manufacturing the product in compliance with cGMP, build a commercial organization, make substantial investments and undertake significant marketing efforts ourselves or in partnership with others. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates.

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If CardioSafe 3D fails to predict accurately and efficiently the cardiac effects, both toxic and nontoxic, of drug rescue candidates and drug rescue NCEs, then our drug rescue programs will be adversely affected.

Our success is partly dependent on our ability to use CardioSafe 3D to identify and predict, accurately and efficiently, the potential toxic and nontoxic cardiac effects of drug rescue candidates and drug rescue NCEs. If CardioSafe 3D is not capable of providing physiologically relevant and clinically predictive information regarding human cardiac biology, our drug rescue business will be adversely affected.

CardioSafe 3D may not be meaningfully more predictive of the behavior of human cells than existing methods.

The success of our drug rescue programs is highly dependent upon CardioSafe 3D being more accurate, efficient and clinically predictive than long-established surrogate safety models, including animal cells and live animals, and immortalized, primary and transformed cells, currently used by pharmaceutical companies and others. We cannot give assurance that CardioSafe 3D will be more efficient or accurate at predicting the heart safety of new drug candidates than the testing models currently used. If CardioSafe 3D fails to provide a meaningful difference compared to existing or new models in predicting the behavior of human heart, respectively, their utility for drug rescue will be limited and our drug rescue business will be adversely affected.

We may invest in producing drug rescue NCEs for which there proves to be no demand.

To generate revenue from our drug rescue activities, we must produce proprietary drug rescue NCEs for which there proves to be demand within the healthcare marketplace, and, if we intend to out-license a particular drug rescue NCE for development and commercialization prior to market approval, then also among pharmaceutical companies and other potential collaborators. However, we may produce drug rescue NCEs for which there proves to be no or limited demand in the healthcare market and/or among pharmaceutical companies and others. If we misinterpret market conditions, underestimate development costs and/or seek to rescue the wrong drug rescue candidates, we may fail to generate sufficient revenue or other value, on our own or in collaboration with others, to justify our investments, and our drug rescue business may be adversely affected.

We may experience difficulty in producing human cells and our future stem cell technology research and development efforts may not be successful within the timeline anticipated, if at all.

Our human pluripotent stem cell technology is technically complex, and the time and resources necessary to develop various human cell types and customized bioassay systems are difficult to predict in advance. We might decide to devote significant personnel and financial resources to research and development activities designed to expand, in the case of drug rescue, and explore, in the case of drug discovery and regenerative medicine, potential applications of our stem cell technology platform. In particular, we may conduct exploratory nonclinical RM programs involving blood, bone, cartilage, heart, and/or liver cells. Although we and our collaborators have developed proprietary protocols for the production of multiple differentiated cell types, we could encounter difficulties in differentiating and producing sufficient quantities of particular cell types, even when following these proprietary protocols. These difficulties could result in delays in production of certain cells, assessment of certain drug rescue candidates and drug rescue NCEs, design and development of certain human cellular assays and performance of certain exploratory nonclinical regenerative medicine studies. In the past, our stem cell research and development projects have been significantly delayed when we encountered unanticipated difficulties in differentiating human pluripotent stem cells into heart and liver cells. Although we have overcome such difficulties in the past, we may have similar delays in the future, and we may not be able to overcome them or obtain any benefits from our future stem cell technology research and development activities. Any delay or failure by us, for example, to produce functional, mature blood, bone, cartilage, and liver cells could have a substantial and material adverse effect on our potential drug discovery, drug rescue and regenerative medicine business opportunities and results of operations.

Restrictions on research and development involving human embryonic stem cells and religious and political pressure regarding such stem cell research and development could impair our ability to conduct or sponsor certain potential collaborative research and development programs and adversely affect our prospects, the market price of our common stock and our business model.

Some of our research and development programs may involve the use of human cells derived from our controlled differentiation of human embryonic stem cells (hESCs). Some believe the use of hESCs gives rise to ethical and social issues regarding the appropriate use of these cells. Our research related to differentiation of hESCs may become the subject of adverse commentary or publicity, which could significantly harm the market price of our common stock. Although now substantially less than in years past, certain political and religious groups in the United States and elsewhere voice opposition to hESC technology and practices. We may use hESCs derived from excess fertilized eggs that have been created for clinical use in in vitro fertilization (IVF) procedures and have been donated for research purposes with the informed consent of the donors after a successful IVF procedure because they are no longer desired or suitable for IVF. Certain academic research institutions have adopted policies regarding the ethical use of human embryonic tissue. These policies may have the effect of limiting the scope of future collaborative research opportunities with such institutions, thereby potentially impairing our ability to conduct certain research and development in this field that we believe is necessary to expand the drug rescue capabilities of our technology, which would have a material adverse effect on our business.

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The use of embryonic or fetal tissue in research (including the derivation of hESCs) in other countries is regulated by the government, and varies widely from country to country. Government-imposed restrictions with respect to use of hESCs in research and development could have a material adverse effect on us by harming our ability to establish critical collaborations, delaying or preventing progress in our research and development, and causing a decrease in the market interest in our stock.

The foregoing potential ethical concerns do not apply to our use of induced pluripotent stem cells (iPSCs) because their derivation does not involve the use of embryonic tissues.

We have assumed that the biological capabilities of iPSCs and hESCs are likely to be comparable. If it is discovered that this assumption is incorrect, our exploratory research and development activities focused on potential regenerative medicine applications of our stem cell technology platform could be harmed.

We may use both hESCs and iPSCs to produce human cells for our customized in vitro assays for drug discovery and drug rescue purposes. However, we anticipate that our future exploratory research and development, if any, focused on potential regenerative medicine applications of our stem cell technology platform primarily will involve iPSCs. With respect to iPSCs, we believe scientists are still somewhat uncertain about the clinical utility, life span, and safety of such cells, and whether such cells differ in any clinically significant ways from hESCs. If we discover that iPSCs will not be useful for whatever reason for potential regenerative medicine programs, this would negatively affect our ability to explore expansion of our platform in that manner, including, in particular, where it would be preferable to use iPSCs to reproduce rather than approximate the effects of certain specific genetic variations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions, which could have a material adverse effect on our operations.

To the extent our research and development activities involve using iPSCs, we will be subject to complex and evolving laws and regulations regarding privacy and informed consent. Many of these laws and regulations are subject to change and uncertain interpretation, and could result in claims, changes to our research and development programs and objectives, increased cost of operations or otherwise harm the Company.

To the extent that we pursue research and development activities involving iPSCs, we will be subject to a variety of laws and regulations in the United States and abroad that involve matters central to such research and development activities, including obligations to seek informed consent from donors for the use of their blood and other tissue to produce, or have produced for us, iPSCs, as well as state and federal laws that protect the privacy of such donors. United States federal and state and foreign laws and regulations are constantly evolving and can be subject to significant change. If we engage in iPSC-related research and development activities in countries other than the United States, we may become subject to foreign laws and regulations relating to human subjects research and other laws and regulations that are often more restrictive than those in the United States. In addition, both the application and interpretation of these laws and regulations are often uncertain, particularly in the rapidly evolving stem cell technology sector in which we operate. These laws and regulations can be costly to comply with and can delay or impede our research and development activities, result in negative publicity, increase our operating costs, require significant management time and attention and subject us to claims or other remedies, including fines or demands that we modify or cease existing business practices.

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Legal, social and ethical concerns surrounding the use of iPSCs, biological materials and genetic information could impair our operations.

To the extent that our future stem cell research and development activities involve the use of iPSCs and the manipulation of human tissue and genetic information, the information we derive from such iPSC-related research and development activities could be used in a variety of applications, which may have underlying legal, social and ethical concerns, including the genetic engineering or modification of human cells, testing for genetic predisposition for certain medical conditions and stem cell banking. Governmental authorities could, for safety, social or other purposes, call for limits on or impose regulations on the use of iPSCs and genetic testing or the manufacture or use of certain biological materials involved in our iPSC-related research and development programs. Such concerns or governmental restrictions could limit our future research and development activities, which could have a material adverse effect on our business, financial condition and results of operations.

Our human cellular bioassay systems and human cells we derive from human pluripotent stem cells, although not currently subject to regulation by the FDA or other regulatory agencies as biological products or drugs, could become subject to regulation in the future.

The human cells we produce from hPSCs and our customized bioassay systems using such cells, including CardioSafe 3D, are not currently sold, for research purposes or any other purpose, to biotechnology or pharmaceutical companies, government research institutions, academic and nonprofit research institutions, medical research organizations or stem cell banks, and they are not therapeutic procedures. As a result, they are not subject to regulation as biological products or drugs by the FDA or comparable agencies in other countries. However, if, in the future, we seek to include human cells we derive from hPSCs in therapeutic applications or product candidates, such applications and/or product candidates would be subject to the FDA's pre- and post-market regulations. For example, if we seek to develop and market human cells we produce for use in performing regenerative medicine applications, such as tissue engineering or organ replacement, we would first need to obtain FDA pre-market clearance or approval. Obtaining such clearance or approval from the FDA is expensive, time-consuming and uncertain, generally requiring many years to obtain, and requiring detailed and comprehensive scientific and clinical data. Notwithstanding the time and expense, these efforts may not result in FDA approval or clearance. Even if we were to obtain regulatory approval or clearance, it may not be for the uses that we believe are important or commercially attractive.

Risks Related to Our Financial Position

We have incurred significant net losses since inception and we will continue to incur substantial operating losses for the foreseeable future. We may never achieve or sustain profitability, which would depress the market price of our common stock, and could cause you to lose all or a part of your investment.

We have incurred significant net losses in each fiscal year since our inception in 1998, including net losses of \$47.2 million and \$13.9 million during the fiscal years ending March 31, 2016 and 2015, respectively. As of March 31, 2016, we had an accumulated deficit of approximately \$131.7 million. We do not know whether or when we will become profitable. Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to incur increasing levels of operating losses over the next several years and for the foreseeable future. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' deficit and working capital. We expect our research and development expenses to significantly increase in connection with non-clinical studies and clinical trials of our product candidates. In addition, if we obtain marketing approval for our product candidates, we may incur significant sales, marketing and outsourced-manufacturing expenses should we elect not to collaborate with one or more third parties for such services and capabilities. As a public company, we incur additional costs associated with operating as a public company. As a result, we expect to

continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenues. To date, we have generated approximately \$16.4 million in revenues, primarily from the receipt of research and development grants from the NIH. We have not yet commercialized any product or generated any revenues from product sales, and we do not know when, or if, we will generate any revenue from product sales. We do not expect to generate significant revenue unless and until we obtain marketing approval of, and begin to experience sales of, AV-101, or we enter into one or more development and commercialization agreements with respect to AV-101 or one or more other product candidates. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

initiate and successfully complete preclinical and clinical trials that meet their prescribed endpoints;

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initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approval for our product candidates;

commercialize our product candidates, if approved, by developing a sales force or entering into collaborations with third parties; and

achieve market acceptance of our product candidates in the medical community and with third-party payors.

Unless we enter into a development and commercialization collaboration or partnership agreement, we expect to incur significant sales and marketing costs as we prepare to commercialize AV-101 or other product candidates. Even if we initiate and successfully complete pivotal clinical trials of AV-101 or other product candidates, and AV-101 or other product candidates are approved for commercial sale, and despite expending these costs, AV-101 or other product candidates may not be commercially successful. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate product revenue, we will not become profitable and may be unable to continue operations without continued funding.

Despite consummation of the May 2016 Public Offering (defined below), we require additional financing to execute our business plan and continue to operate as a going concern.

Our consolidated financial statements for the year ended March 31, 2016 have been prepared assuming we will continue to operate as a going concern. Because we continue to experience net operating losses, our ability to continue as a going concern is subject to our ability to obtain necessary funding from outside sources, including obtaining additional funding from the sale of our securities or obtaining loans and grants from financial institutions and/or government agencies where possible. Our continued net operating losses increase the difficulty in completing such sales or securing alternative sources of funding, and there can be no assurances that we will be able to obtain such funding on favorable terms or at all. If we are unable to obtain sufficient financing from the sale of our securities or from alternative sources, we may be required to reduce, defer, or discontinue certain or all of our research and development activities or we may not be able to continue as a going concern.

Since our inception, most of our resources have been dedicated to research and development of AV-101 and the drug rescue capabilities of our stem cell technology platform. In particular, we have expended substantial resources advancing AV-101 through preclinical development and Phase 1 clinical safety studies, and developing CardioSafe 3D for drug rescue applications, and we will continue to expend substantial resources for the foreseeable future developing and commercializing AV-101, and, potentially, developing drug rescue NCEs and RM therapies. These expenditures will include costs associated with general and administrative costs, facilities costs, research and development, acquiring new technologies, manufacturing product candidates, conducting preclinical experiments and clinical trials and obtaining regulatory approvals, as well as commercializing any products approved for sale.

At March 31, 2016, our existing cash and cash equivalents were not sufficient to fund our current operations for the next 12 months. As described in Note 16, Subsequent Events, to the accompanying Consolidated Financial Statements for the fiscal year ended March 31, 2016 included elsewhere in this Annual Report, on May 16, 2016, we consummated an underwritten public offering, pursuant to which we issued an aggregate of 2,570,040 registered shares of our common stock at a public sales price of \$4.24 per share and five-year warrants, exercisable at \$5.30 per share, to purchase an aggregate of 2,705,883 shares of our common stock at a public sales price of \$0.01 per warrant share, including shares and warrants issued pursuant to the exercise of the underwriters' over-allotment option, resulting in gross proceeds of \$10,924,000 (May 2016 Public Offering). Our net proceeds from the May 2016 Public Offering were approximately \$9.5 million after deducting underwriters' commissions and other expenses of the offering. Additionally, in February 2015, we entered into the CRADA with the NIH, under which the NIH is fully funding and conducting the initial Phase 2a clinical efficacy and safety of AV-101 in MDD. However, we have no

current source of revenue to sustain our present activities, and we do not expect to generate revenue until, and unless, we (i) out-license or sell AV-101, a drug rescue NCE, and/or another drug candidate unrelated to AV-101 to third-parties, (ii) enter into license arrangements involving our stem cell technology, or (iii) obtain approval from the FDA or other regulatory authorities and successfully commercialize, on our own or through a future collaboration, one or more of our compounds.

As the outcome of our AV-101 and NCE drug rescue activities and future anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates, on our own or in collaboration with others. In addition, other unanticipated costs may arise. As a result of these and other factors, we will need to seek additional capital in the near term to meet our future operating requirements, including capital necessary to obtain regulatory approval for, and to commercialize, our product candidates, and may seek additional capital in the event there exists favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. We are considering a range of potential sources of funding, including public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches, and we may complete additional financing arrangements in 2016. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

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Our future capital requirements depend on many factors, including:

the number and characteristics of the product candidates we pursue, including AV-101 and drug rescue NCEs;

the scope, progress, results and costs of researching and developing our product candidates, and conducting preclinical and clinical studies;

the timing of, and the costs involved in, obtaining regulatory approvals for our product candidates;

the cost of commercialization activities if any of our product candidates are approved for sale, including marketing, sales and distribution costs;

the cost of manufacturing our product candidates and any products we successfully commercialize;

our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;

market acceptance of our products;

the effect of competing technological and market developments;

our ability to obtain government funding for our programs;

the costs involved in obtaining and enforcing patents to preserve our intellectual property;

the costs involved in defending against such claims that we infringe third-party patents or violate other intellectual property rights and the outcome of such litigation;

the timing, receipt and amount of potential future licensee fees, milestone payments, and sales of, or royalties on, our future products, if any; and

the extent to which we acquire or invest in businesses, products and technologies, although we currently have no commitments or agreements relating to any of these types of transactions.

Any additional fundraising efforts will divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts, in a timely manner, or on terms acceptable to us, if at all, and the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity securities and the conversion or exchange of certain of our outstanding securities will dilute all of our stockholders. The incurrence of debt could result in increased fixed payment obligations and we could be required to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidate or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain additional funding on a timely basis and on acceptable terms, we may be required to significantly curtail, delay or discontinue one or more of our research or product development programs or the commercialization of any product candidate or be unable to continue or expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

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Proceeds from the May 2016 Public Offering will not be sufficient to complete the Phase 2b MDD Study, resulting in the need for additional financing.

Although we anticipate that the net proceeds from the May 2016 Public Offering will provide sufficient funding for our operations through the release of topline results of our fully-funded, NIH-sponsored AV-101 Phase 2a clinical study in MDD (Phase 2a MDD Study), anticipated in the second quarter of 2017, as well as the launch and conduct of a substantial portion of our AV-101 Phase 2b clinical study in MDD (Phase 2b MDD Study), the proceeds received will not be sufficient to complete the Phase 2b MDD Study, unless we also receive, prior to the end of the second quarter of 2017, proceeds resulting from the exercise of a substantial portion of the warrants offered in the May 2016 Public Offering and the underwriters exercise their option to purchase additional shares of common stock. Assuming no exercise of the warrants issued in the May 2016 Public Offering and no exercise of the underwriters' option to purchase additional shares of common stock, we believe an additional \$10.0 million to \$12.0 million will be required prior to the end of the second quarter of 2017 in order to complete the Phase 2b MDD Study before the second half of 2018. No assurances can be provided that such additional capital will be available to us when necessary, on reasonable terms, or at all. In the event we are unable to raise such additional capital, our operations, including the conduct of the Phase 2b MDD Study, will be negatively and materially affected

Raising additional capital will cause dilution to our existing stockholders, and may restrict our operations or require us to relinquish rights.

We intend to pursue private and public equity offerings, debt financings, collaborations and licensing arrangements in 2016 and beyond. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, or to the extent, for strategic purposes, we convert or exchange certain of our outstanding securities into common stock, our current stockholders' ownership interest in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect rights of our stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic partnerships and licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, our intellectual property, future revenue streams or grant licenses on terms that are not favorable to us.

Some of our programs have been partially supported by government grants, which may not be available to us in the future.

Since inception, we have received substantial funds under grant award programs funded by state and federal governmental agencies, such as the NIH, the NIH's National Institute of Neurological Disease and Stroke and the NIH's National Institute of Mental Health, and the California Institute for Regenerative Medicine. To fund a portion of our future research and development programs, we may apply for additional grant funding from such or similar governmental organizations. However, funding by these governmental organizations may be significantly reduced or eliminated in the future for a number of reasons. For example, some programs are subject to a yearly appropriations process in Congress. In addition, we may not receive funds under future grants because of budgeting constraints of the agency administering the program. Therefore, we cannot assure you that we will receive any future grant funding from any government organization or otherwise. A restriction on the government funding available to us could reduce the resources that we would be able to devote to future research and development efforts. Such a reduction could delay the introduction of new products and hurt our competitive position.

Our ability to use net operating losses to offset future taxable income is subject to certain limitations.

As of March 31, 2016, we had federal and state net operating loss carryforwards of \$67.9 million and \$60.1 million, respectively, which begin to expire in fiscal 2017. Under Section 382 of the Internal Revenue Code of 1986, as amended (the Code) changes in our ownership may limit the amount of our net operating loss carryforwards that could be utilized annually to offset our future taxable income, if any. This limitation would generally apply in the event of a cumulative change in ownership of our company of more than 50% within a three-year period. Any such limitation may significantly reduce our ability to utilize our net operating loss carryforwards and tax credit carryforwards before they expire. Any such limitation, whether as the result of future offerings, prior private placements, sales of our common stock by our existing stockholders or additional sales of our common stock by us in the future, could have a material adverse effect on our results of operations in future years. We have not completed a study to assess whether an ownership change for purposes of Section 382 has occurred, or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such study.

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General Company-Related Risks

If we fail to attract and retain senior management and key scientific personnel, we may be unable to successfully produce, develop and commercialize AV-101, drug rescue NCEs, other potential product candidates and other commercial applications of our stem cell technology.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management and scientific and technical personnel. We are highly dependent upon our Chief Executive Officer, President and Chief Scientific Officer, Chief Medical Officer and Chief Financial Officer, as well as other employees, consultants and scientific collaborators. As of the date of this Annual Report, we have nine full-time employees, which may make us more reliant on our individual employees than companies with a greater number of employees. The loss of services of any of these individuals could delay or prevent the successful development of AV-101, drug rescue NCEs, other product candidates, and other applications of our stem cell technology, including our production and assessment of potential drug rescue NCEs or disrupt our administrative functions.

Although we have not historically experienced unique difficulties attracting and retaining qualified employees, we could experience such problems in the future. For example, competition for qualified personnel in the biotechnology and pharmaceuticals field is intense. We will need to hire additional personnel as we expand our research and development and administrative activities. We may not be able to attract and retain quality personnel on acceptable terms.

In addition, we rely on a diverse range of strategic consultants and advisors, including manufacturing, scientific and clinical development, and regulatory advisors, to assist us in designing and implementing our research and development and regulatory strategies and plans, including our AV-101 development and drug rescue strategies and plans. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

As we seek to advance development of AV-101 for MDD and other CNS-related conditions, as well as drug rescue and stem cell technology-related RM programs, we will need to expand our research and development capabilities and/or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners and other third parties. Future growth will impose significant added responsibilities on members of management. Our future financial performance and our ability to develop and commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our research and development efforts effectively and hire, train and integrate additional management, administrative and technical personnel. The hiring, training and integration of new employees may be more difficult, costly and/or time-consuming for us because we have fewer resources than a larger organization. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing the company.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

If we develop AV-101, drug rescue NCEs, other product candidates, or regenerative medicine product candidates, either on our own or in collaboration with others, we will face inherent risks of product liability as a result of the required clinical testing of such product candidates, and will face an even greater risk if we or our collaborators commercialize any such product candidates. For example, we may be sued if AV-101, any drug rescue NCE, other product candidate, or regenerative medicine product candidate we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product,

negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

decreased demand for products that we may develop;

injury to our reputation;

withdrawal of clinical trial participants;

costs to defend the related litigation;

a diversion of management's time and our resources;

substantial monetary awards to trial participants or patients;

product recalls, withdrawals or labeling, marketing or promotional restrictions;

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loss of revenue;

the inability to commercialize our product candidates; and

a decline in our stock price.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. Although we maintain liability insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

As a public company, we incur significant administrative workload and expenses to comply with U.S. regulations and requirements imposed by The NASDAQ Stock Market concerning corporate governance and public disclosure.

As a public company with common stock listed on The NASDAQ Capital Market, we must comply with various laws, regulations and requirements, including certain provisions of the Sarbanes-Oxley Act of 2002, as well as rules implemented by the SEC and The NASDAQ Stock Market. Complying with these statutes, regulations and requirements, including our public company reporting requirements, continues to occupy a significant amount of the time of management and involves significant accounting, legal and other expenses. Furthermore, these laws, regulations and requirements require us to observe greater corporate governance practices than we have employed in the past, including, but not limited to maintaining a sufficient number of independent directors, increased frequency of board meetings, and holding annual stockholder meetings. Our efforts to comply with these regulations are likely to result in increased general and administrative expenses and management time and attention directed to compliance activities.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial and stock markets. Global financial crises cause extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the recent global financial crisis, could result in a variety of risks to our business, including, weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We or the third parties upon whom we depend may be adversely affected by natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party CMOs, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and

business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business.

Our internal computer systems, or those of our third-party CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product candidates' development programs.

Despite the implementation of security measures, our internal computer systems and those of our third-party CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such system failure, accident, or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for AV-101 or other product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed.

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We may acquire businesses or products, or form strategic alliances, in the future, and we may not realize the benefits of such acquisitions.

We may acquire additional businesses or products, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

Risks Related to Our Intellectual Property Rights

If we are unable to adequately protect our proprietary technology, or obtain and maintain issued patents that are sufficient to protect our product candidates, others could compete against us more directly, which would have a material adverse impact on our business, results of operations, financial condition and prospects.

We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking patents intended to cover our products and compositions, their methods of use and any other inventions we consider are important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, to defend and enforce our patents, should they issue, to preserve the confidentiality of our trade secrets and to operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain the proprietary position of our product candidates. We own patent applications related to AV-101 and we own and have licensed patents and patent applications related to human pluripotent stem cell technology.

We currently have no issued patents covering AV-101. We cannot provide any assurances that any of our numerous pending U.S. and foreign patent applications relating to AV-101 will mature into issued patents and, if they do, that such patents will include claims with a scope sufficient to protect AV-101 or otherwise provide any competitive advantage. Moreover, other parties may have developed technologies that may be related or competitive to our approach, and may have filed or may file patent applications and may have received or may receive patents that may overlap or conflict with our patent applications, either by claiming the same methods or formulations or by claiming subject matter that could dominate our patent position. Such third-party patent positions may limit or even eliminate our ability to obtain patent protection.

The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, and, therefore, the issuance, scope, validity and enforceability of any patent claims that we may obtain cannot be predicted with certainty. Patents, if issued, may be challenged, deemed unenforceable, invalidated, or circumvented. U.S. patents and patent applications may also be subject to interference proceedings, ex parte reexamination, or inter partes review proceedings, supplemental examination and challenges in district court. Patents may be subjected to opposition, post-grant review, or comparable proceedings lodged in various foreign, both national and regional, patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such proceedings may be costly. Thus, any patents, should they issue, that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference

proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize our product candidates.

Furthermore, though a patent, if it were to issue, is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products. Even if a patent issues and is held to be valid and enforceable, competitors may be able to design around our patents, such as using pre-existing or newly developed technology. Other parties may develop and obtain patent protection for more effective technologies, designs or methods. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, vendors, former employees and current employees. The laws of some foreign countries do not protect our proprietary rights to the same extent as the laws of the United States, and we may encounter significant problems in protecting our proprietary rights in these countries. If these developments were to occur, they could have a material adverse effect on our sales.

Our ability to enforce our patent rights depends on our ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's