

VistaGen Therapeutics, Inc.
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Prospectus

Dated August 31, 2015

3,992,479 Shares of Common Stock

VISTAGEN THERAPEUTICS, INC.

We are registering for resale up to 3,992,479 shares of common stock, \$0.001 per share, of VistaGen Therapeutics, Inc. (“we,” “us,” or the “Company”), held by the selling stockholders listed beginning on page 115 of this prospectus (“Selling Stockholders”). All of the shares being registered are being or may be offered for resale by the Selling Stockholders. The shares of common stock registered for potential resale by the selling stockholders under this prospectus include:

- up to 2,951,688 shares of common stock issuable upon conversion of shares of Series B 10% Convertible Preferred Stock (“Series B Preferred”) issued in a series of self-placed private placement transactions, the first of which was consummated on May 12, 2015 (the “Private Placements”); and
- up to 1,040,791 shares of common stock issuable upon exercise of warrants to purchase common stock (“Warrants”) issued in connection with the Private Placements.

We will not receive any proceeds from the resale of any shares of common stock by the Selling Stockholders under this prospectus. However, if Warrants are exercised by the Selling Stockholders who hold them, we will receive the exercise price of any such Warrant exercises. We will pay the expenses of registering the shares of common stock for resale by the Selling Stockholders under this prospectus. See “Selling Stockholders” beginning on page 115 of this prospectus for a list of the Selling Stockholders.

The shares of common stock are being registered to provide the Selling Stockholders the opportunity to resell the shares from time to time, in amounts and at prices and on terms they may determine at the time of the offering. The Selling Stockholders may resell the shares of our common stock covered by this prospectus in a number of different ways and at prevailing market prices or privately negotiated transactions. We provide more information about how the Selling Stockholders may resell their shares in the section entitled “Plan of Distribution” beginning on page 118 of this prospectus.

Our common stock is quoted on the OTCQB under the symbol “VSTA.” The last reported sale price of our common stock on August 28, 2015 was \$11.00 per share.

No underwriter or other person has been engaged to facilitate the resale of shares of common stock or exercise of Warrants by the Selling Stockholders under this prospectus.

You should rely only on the information contained in this prospectus. We have not, and the Selling Stockholders have not, authorized anyone to provide you with different information. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained in this prospectus. You must not rely on any unauthorized information or representations. If anyone provides you with different information, you should not rely on

it. We are not, and the Selling Stockholders are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information contained in this prospectus is accurate only as of the date on the front cover of this prospectus. Our business, financial condition, results of operations and prospects may have changed since that date.

Investing in our common stock involves a high degree of risk. See “Risk Factors” beginning on page 3 of this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is August 31, 2015.

VistaGen Therapeutics, Inc.

TABLE OF CONTENTS

	Page
<u>Prospectus Summary</u>	2
<u>The Offering</u>	2
<u>Risk Factors</u>	3
<u>Use of Proceeds</u>	33
<u>Special Note Regarding Forward-Looking Statements</u>	33
<u>Business</u>	34
<u>Legal Proceedings</u>	73
<u>Market Price of Common Stock and Other Stockholder Matters</u>	74
<u>Selected Consolidated Financial Data</u>	75
<u>Management's Discussion and Analysis of Financial Condition and Results of Operations</u>	75
<u>Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</u>	93
<u>Directors, Executive Officers, Promoters and Control Persons</u>	97
<u>Executive Compensation</u>	98
<u>Certain Relationships and Related Transactions</u>	105
<u>Security Ownership of Certain Beneficial Owners and Management and Related Stockholders Matters</u>	106
<u>Description of Securities to be Registered</u>	113
<u>Selling Stockholders</u>	115
<u>Relationships Between the Issuer and the Selling Security Holders</u>	118
<u>Plan of Distribution</u>	118
<u>Experts</u>	119
<u>Legal Matters</u>	120
<u>Interests of Named Experts and Counsel</u>	120
<u>Where You Can Find More Information</u>	120
<u>Index to Consolidated Financial Statements for the years ended March 31, 2015 and 2014, and Condensed Consolidated Financial Statements for the three months ended June 30, 2015 and 2014</u>	F-1

You should rely only on the information contained in this prospectus. We have not authorized anyone to provide you with additional information or information different from that contained in this prospectus. The information contained in this prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or any sale of our common stock.

We own or have rights to use a number of common law trademarks and trade names that we use in connection with our business, including VistaGen Therapeutics, Inc., VistaGen, our logo, Better Cells Lead to Better Medicine, Human Clinical Trials in a Test Tube, CardioSafe 3D and LiverSafe 3D. Solely for convenience, the trademarks and trade names referred to in certain portions of this prospectus may have been included without the TM symbol, but any such references are not intended to indicate in any way that we will not assert to the fullest extent under applicable law our rights to use those trademarks and trade names. All other trademarks, service marks and trade names referred to in this prospectus, if any, are, to our knowledge, the property of their respective owners.

Unless the context otherwise requires, the words “VistaGen Therapeutics, Inc.” “VistaGen,” “we,” “the Company,” “us” and “our” refer to VistaGen Therapeutics, Inc., a Nevada corporation. “VistaGen California” refers to VistaGen Therapeutics, Inc., a California corporation and our wholly owned subsidiary.

Table of Contents

FORWARD-LOOKING STATEMENTS

This prospectus, including the information incorporated by reference, contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995. The use of any statements containing the words “intend,” “believe,” “estimate,” “project,” “expect,” “anticipate,” “plan,” “should” or similar expressions are intended to identify forward-looking statements. Forward-looking statements inherently involve risks and uncertainties that could cause actual results to differ materially from the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, changes in demand for our products and services, changes in the level of operating expenses, our ability to execute our business and operating plan, changes in general economic conditions that impact government spending, regulatory issues, dependence on third party suppliers, and other risks detailed in this prospectus under the heading “Risk Factors” and in our periodic report filings with the Securities and Exchange Commission (the “SEC”).

Forward-looking statements are subject to numerous assumptions, risks and uncertainties, which change over time. Forward-looking statements speak only as of the date they are made, and we assume no duty to and do not undertake to update forward-looking statements. These forward-looking statements may not meet the safe harbor for forward-looking statements pursuant to Sections 21E or 27A of the Securities Act. Actual results could differ materially from those anticipated in forward-looking statements and future results could differ materially from historical performance.

Table of Contents

PROSPECTUS SUMMARY

This summary highlights information contained elsewhere in this prospectus. This summary does not contain all the information you should consider before buying our common stock. You should read the following summary together with the more detailed information appearing in this prospectus, including our Consolidated Financial Statements for the years ended March 31, 2015 and 2014, and the Condensed Consolidated Financial Statements for the three months ended June 30, 2015 and 2014, and related notes thereto, as well as our risk factors beginning on page 3, before deciding whether to purchase shares of our common stock.

Overview

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

More than one billion people worldwide suffer from CNS disorders. Recently, the economic burden of these disorders was estimated at \$2.0 trillion in the U.S. and European Union alone, a figure that is expected to triple by 2030. The World Health Organization 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. In 2012, the NIH estimated 16 million adults aged 18 or older in the U.S. had at least one major depressive episode. This represented approximately 6.7 percent of all U.S. adults.

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

Following two successful randomized, double-blind, placebo-controlled Phase 1 safety studies funded by the NIH, in February 2015, we entered into a Cooperative Research and Development Agreement (“CRADA”) with the U.S. National Institute of Mental Health (“NIMH”), part of the NIH. Under the CRADA, we will collaborate with the NIMH on the initial Phase 2 clinical study of AV-101 in subjects with treatment-resistant MDD. Pursuant to the CRADA, the study will be conducted at the NIMH and be fully funded by the NIMH. It is contemplated that this clinical study will begin in Fall 2015 under the direction of Dr. Carlos Zarate, Jr., the NIMH’s Chief of Experimental Therapeutics & Pathophysiology Branch and of the Section on Neurobiology and Treatment of Mood and Anxiety Disorders.

In addition to developing AV-101 for MDD and other CNS indications, we are applying our stem cell technology for drug rescue programs intended to identify and develop proprietary new chemical entities (“NCEs”) for our internal drug candidate pipeline. Drug rescue involves (1) using our customized in vitro bioassay systems to predict potential heart and liver toxicity of NCEs, (2) leveraging prior investments by pharmaceutical companies and others related to screening large-scale compound libraries, optimizing and testing for efficacy NCEs that were terminated before FDA approval due to heart or liver toxicity and are now available in the public domain, and (3) applying modern medicinal

chemistry to produce safer NCEs for our internal development pipeline. Our CardioSafe 3D™ bioassay system uses our human pluripotent stem cell (“hPSC”)-derived cardiomyocytes, or human heart cells. We believe CardioSafe 3D is more comprehensive and clinically predictive than the hERG assay, which is currently the only in vitro cardiac safety assay required by FDA guidelines. We use our hPSC-derived hepatocytes, or human liver cells, in our LiverSafe 3D™ bioassay system to predict potential liver toxicity of NCEs, including potential drug metabolism issues and adverse drug-drug interactions. CardioSafe 3D and LiverSafe 3D offer a new paradigm for evaluating and predicting potential heart and liver toxicity of NCEs, including drug rescue NCEs, early in the development process, long before costly, high risk animal studies and human clinical trials. We intend to develop internally for our pipeline each lead drug rescue NCE we produce.

THE OFFERING

Securities Offered by the Selling Stockholders	3,992,479 shares of common stock.
Common Stock Outstanding as of August 24, 2015	1,594,461 shares.
Use of Proceeds	We will not receive any of the proceeds of the shares of common stock which may be offered for resale by the Selling Stockholders. If Warrants held by certain of which may be the Selling Stockholders are exercised, we will receive the exercise proceeds from such exercises. The shares of common stock that may be resold by the Selling Stockholders under this prospectus are issuable upon the conversion of securities sold by us to the Selling Stockholders in a series of self-placed private placement transactions, or upon future exercise of Warrants.
Risk Factors	Prior to making an investment decision, you should carefully consider all of the information in this prospectus and, in particular, you should evaluate the risk factors set forth under the caption “Risk Factors” beginning on page 3.
Trading Symbol	VSTA

Table of Contents

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 Prospectus 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 non-clinical and clinical development, regulatory approval and commercialization of AV-101 for depression, including Major Depressive Disorder (“MDD”), and various other diseases and disorders involving the central nervous system (“CNS”), as well as our ability to produce, develop and commercialize new chemical entities (“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. 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 U.S. Food and Drug Administration, or 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 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, or an NDA, from the FDA, or in any foreign countries until we receive the requisite approval from such countries. We recently received FDA clearance to initiate the initial Phase 2 clinical trial involving AV-101, to study its safety, tolerability and efficacy in patients with MDD. If our Phase 2 clinical trial of AV-101 is successful, we expect the FDA to require us to complete at least one additional Phase 2 clinical trial and at least one pivotal Phase 3 clinical trial in order to submit an NDA for AV-101 as a treatment for MDD. However, the FDA may require that we conduct more than one additional Phase 2 clinical study and more than one Phase 3 pivotal trial of AV-101 before we can submit an NDA. The FDA may also 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:

- we may not be able to demonstrate that the product candidate is safe and effective in treating a human disease or disorder, to the satisfaction of the FDA;
- the results of our non-clinical studies and clinical trials may not meet the level of statistical or clinical significance required by the FDA for marketing approval;
- the FDA may disagree with the number, design, size, conduct or implementation of our non-clinical studies and clinical trials;
- the FDA may require that we conduct additional non-clinical studies and clinical trials;
- the FDA or the applicable foreign regulatory agency may not approve the formulation, labeling or specifications of any of our product candidates;
- the contract research organizations, or CROs, that we retain to conduct our non-clinical studies and clinical trials may take actions outside of our control that materially adversely impact our non-clinical studies and clinical trials;
- the FDA may find the data from non-clinical studies and clinical trials insufficient to demonstrate that our product candidates' clinical and other benefits outweigh their safety risks;
- the FDA may disagree with our interpretation of data from our non-clinical studies and clinical trials;
- the FDA may not accept data generated at our non-clinical studies and clinical trial sites;
- 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, or 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, or cGMPs; or
- the FDA or applicable foreign regulatory agency may change its approval policies or adopt new regulations.

Table of Contents

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain regulatory approval for and successfully market 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.

A Fast Track designation by the FDA may not actually lead to a faster development or regulatory review or approval process.

We intend to seek FDA Fast Track designation for AV-101, and we may do so for other product candidates as well. If a product candidate is intended for the treatment of a serious or life-threatening condition and the product candidate demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for the FDA Fast Track designation. 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 may encounter difficulties in enrolling patients in our AV-101 clinical trials, including our impending NIH-funded Phase 2 clinical study of AV-101 in MDD, thereby delaying or preventing clinical development. Further, if AV-101 is approved for 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.

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

AV-101 will be tested in an NIH investigator sponsored Phase 2 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.

-4-

Table of Contents

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

Positive results from non-clinical 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 non-clinical studies and clinical trials. Similarly, even if we are able to complete our planned non-clinical studies or clinical trials of our product candidates according to our current development timeline, the positive results from our non-clinical studies and clinical trials of our product candidates may not be replicated in subsequent non-clinical 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, non-clinical findings made while clinical trials were underway or safety or efficacy observations made in non-clinical studies and clinical trials, including previously unreported adverse events. Moreover, non-clinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in non-clinical studies and clinical trials nonetheless failed to obtain FDA approval. We have not yet completed any Phase 2 clinical trial for AV-101, and if we fail to produce positive results in our NIH-sponsored Phase 2 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, would 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.

We and the NIH are preparing to commence an NIH-funded Phase 2 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 2 study of AV-101 or any of our future-planned clinical trials will begin or 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 non-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, or 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;
- 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 non-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.

Table of Contents

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, or 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 non-clinical studies and clinical trials of our product candidates may occur, which may result in changes to non-clinical studies and clinical trial protocols or additional non-clinical 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 non-clinical studies and clinical trials may force us to amend non-clinical studies and clinical trial protocols or the FDA may impose additional non-clinical 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 non-clinical studies may adversely impact the cost, timing, or successful completion of those non-clinical studies. If we experience delays completing, or if we terminate, any of our non-clinical studies or clinical trials, or if we are required to conduct additional non-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 contract research organizations, or 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;
- 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 NIH are required to comply with regulations and guidelines, including current Good Clinical Practices, or 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.

Table of Contents

Although we intend to design our clinical trials for our product candidates, we plan to have CROs, and in the case of our initial AV-101 Phase 2 study in MDD, the NIH, conduct all of the 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 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 non-clinical 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.

We do not have long-term supply agreements in place with our contract manufacturers and each batch of our product candidates is 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 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 non-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.

Table of Contents

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. In order to market our product candidates, if approved by the FDA or any other regulatory body, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, 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 CNS 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;
- 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 non-clinical 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.

Table of Contents

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 “boxed” 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.

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.

Table of Contents

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

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, management is unaware of any FDA-approved therapy for MDD with the mechanism of action of AV-101. However, products approved for other indications, for example, 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 treatment options, such as psychotherapy and electroconvulsive therapy, or ECT, are sometimes used before or instead of antidepressant medications to treat patients with MDD.

In the field of new generation antidepressants focused on modulation of the NMDA receptor, our principal competitor is Naurex, Inc., which is developing GLYX-13 and NRX-1074 for treatment-resistant MDD. Although each of these drug candidates is a peptide and may not be orally active in MDD patients (GLYX-13 is only administered intravenously and, we believe, NRX-1074 has not yet been administered orally to MDD patients), both are new generation NMDA modulators focused, as is AV-101, on the glycine binding 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 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, Actavis, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Roche, Sumitomo Dainippon, 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.

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 a 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.

Table of Contents

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 collaborations 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 biopharmaceutical product candidates. Although AV-101 is in Phase 2 clinical development, our research programs, we may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential 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.

Because we have limited financial and management resources, we focus on a limited number of research programs and product candidates and are currently focused on AV-101 and stem cell technology-based drug rescue . As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications 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:

-11-

Table of Contents

- 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.

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 AV0-101 as a treatment 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.

Table of Contents

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 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.

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.

Table of Contents

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 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.

Our future success is highly dependent upon our ability to successfully develop and commercialize AV-101 and produce, develop and commercialize proprietary NCEs using our stem cell technology, human cells derived from stem cells, our customized human cell-based bioassay systems and medicinal chemistry, 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.

Table of Contents

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 for internal development or out-license to pharmaceutical companies and others, 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 or LiverSafe 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 a strategic collaboration. Before we generate any revenues from AV-101 and/or additional drug rescue NCEs we or our potential strategic collaborator 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.

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 highly 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.

We have not yet fully validated LiverSafe 3D for potential drug rescue applications, and we may never do so.

We have developed proprietary protocols for controlling the differentiation of human pluripotent stem cells and producing functional, mature, adult liver cells we believe are superior to primary (cadaver) hepatocytes used in in vitro testing. However, we have not yet fully validated our ability to use the human liver cells we produce for LiverSafe 3D to predict important biological effects, both toxic and nontoxic, of reference drugs, drug rescue candidates or drug rescue NCEs on the human liver, including drug-induced liver injury and adverse drug-drug interactions. Furthermore, we may never be able to do so, which could adversely affect our business and the potential applications of LiverSafe 3D for drug discovery, drug rescue and regenerative medicine.

CardioSafe 3D, and, if validated, LiverSafe 3D may not be meaningfully more predictive of the behavior of human cells than existing methods.

The success of our drug rescue business is highly dependent, in the first instance, upon CardioSafe 3D, and, in the second instance, if validated, LiverSafe 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, and, when validated, LiverSafe 3D, will be more efficient or accurate at predicting the heart or liver safety of new drug candidates than the testing models currently used. If CardioSafe 3D and LiverSafe 3D fail to provide a meaningful difference compared to existing or new models in predicting the behavior of human heart and liver cells, respectively, their utility for drug rescue will be limited and our drug rescue business will be adversely affected.

Table of Contents

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 strategic 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 research and development programs related to producing and using functional, mature adult liver cells to validate LiverSafe 3D as a novel bioassay system for drug rescue, as well as exploratory nonclinical regenerative medicine programs involving blood, bone, cartilage, heart, and liver. Although we and our collaborators have developed proprietary protocols for the production of multiple differentiated cell types, we could encounter difficulties in differentiating 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 ongoing and planned research and development programs 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 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.

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. These potential ethical concerns do not apply to induced pluripotent stem cells (“iPSCs”), or our plans to pursue studies involving human cells derived from iPSCs, because their derivation does not involve the use of embryonic tissues.

Table of Contents

We have assumed that the biological capabilities of induced pluripotent stem cells (“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 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 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 induced pluripotent stem cells, 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.

-17-

Table of Contents

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 and LiverSafe 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 cell therapy or for other 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.

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 and Chief Financial Officer, as well as other employees, consultants and scientific collaborators. As of the date of this prospectus, 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 potential 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 consultants and advisors, including scientific and clinical development advisors, to assist us in designing our research and development strategies, 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.

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance development of AV-101 for MDD and other CNS-related conditions, as well as cell production, bioassay development, drug discovery, drug rescue and development unrelated to AV-101, and stem cell technology-related regenerative medicine programs, we will need to expand our research and development capabilities 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.

Table of Contents

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 an 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;
- 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 we continue to grow, we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

As we continue to grow our organization and seek to obtain listing of our common stock on a national securities market, we will need to establish and maintain more elaborate disclosure and financial controls and make changes in

our corporate governance practices. We will need to hire additional accounting and financial personnel with appropriate public company experience and technical accounting knowledge, and it may be difficult to recruit and retain such personnel. Even if we are able to hire appropriate personnel, our existing operating expenses and operations will increase by the direct costs of their employment and the indirect consequences related to the diversion of management resources from product development efforts.

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 markets. The recent global financial crisis caused 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.

Table of Contents

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 our 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.

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 Financial Position and Need for Capital

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 \$13.9 million and \$3.0 million during the fiscal years ending March 31, 2015 and 2014, respectively. As of June 30, 2015, we had an accumulated deficit of \$114.0 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 will incur significant sales, marketing and outsourced-manufacturing expenses. 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.

Table of Contents

Our ability to become profitable depends upon our ability to generate revenues. To date, although we have generated approximately \$16.4 million in revenues, we have not commercialized any products 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 sell, AV-101, or we enter into one or more strategic development and commercialization agreements with respect to AV-101 or another product candidate. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- initiate and successfully complete clinical trials that meet their clinical endpoints;
 - 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.
- Absent our entering into a strategic development and commercialization collaboration or partnership agreement, we expect to incur significant sales and marketing costs as we prepare to commercialize our product candidates. Even if we initiate and successfully complete pivotal clinical trials of our product candidates, and our product candidates are approved for commercial sale, and despite expending these costs, our product candidates may not be a commercially successful drug. 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.

Our independent auditors have expressed substantial doubt about our ability to continue as a going concern.

Our Consolidated Financial Statements for the years ended March 31, 2015 and 2014 included in this prospectus have been prepared assuming we will continue to operate as a going concern. However, due to our ongoing operating losses and our accumulated deficit, in their opinion on our audited financial statements for our fiscal year ended March 31, 2015, our auditors indicated that there is substantial doubt about our ability to continue 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 of our research and development activities or we may not be able to continue as a going concern.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts or other operations.

Since our inception, most of our resources have been dedicated to research and development of AV-101 and the drug rescue capabilities of our human pluripotent 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 and LiverSafe 3D for drug rescue applications, and we will continue to expend substantial resources for the foreseeable future developing and commercializing AV-101, validating LiverSafe 3D, and

developing drug rescue NCEs. 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 June 30, 2015, our existing cash and cash equivalents were not sufficient to fund our current operations for the next 12 months. Although, in February 2015, we entered into a Cooperative Research and Development Agreement (“CRADA”) with the U.S. National Institutes of Health (“NIH”), under which CRADA the NIH will fully fund and conduct the initial Phase 2 clinical efficacy and safety of AV-101 in Major Depressive Disorder at no cost to us, 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, another drug candidate unrelated to AV-101 to third-parties, (ii) enter into license arrangements involving our stem cell technology, including customized drug discovery and predictive toxicology assays and services and/or regenerative medicine opportunities with a third party, 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 proposed drug rescue and AV-101 development 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 intend to complete additional financing arrangements prior to the end of 2015. 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.

Table of Contents

Our future capital requirements depend on many factors, including:

- the number and characteristics of the product candidates we pursue, including AV-101 or 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 preparing, filing, prosecuting, maintaining, defending and enforcing patent claims necessary to preserve our freedom to operate in the stem cell industry, including litigation costs associated with any 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 or convertible securities would also dilute all of our stockholders. The incurrence of indebtedness 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 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.

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

We intend to seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, your 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 your rights as a stockholder. 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.

Table of Contents

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 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, 2015, we had federal and state net operating loss carryforwards of \$58.7 million and \$53.1 million, respectively, which begin to expire in fiscal 2016. Under Section 382 of the Internal Revenue Code of 1986, as amended, or 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.

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, defend and enforce our patents, should they issue, preserve the confidentiality of our trade secrets and 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. Our owned and licensed patents and patent applications relate to AV-101 and, in general, human pluripotent stem cell technology.

We currently have no issued patents covering AV-101. We cannot provide any assurances that any of our multiple 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 for certain inventories.

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.

Table of Contents

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 or potential competitor's product. Any litigation to enforce or defend our patent rights, even if we were to prevail, could be costly and time-consuming and would divert the attention of our management and key personnel from our business operations. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

In addition, proceedings to enforce or defend our patents, if and when issued, could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of our patents are invalid or otherwise unenforceable. If any of our patents, if and when issued, covering our product candidates are invalidated or found unenforceable, our financial position and results of operations would be materially and adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered our product candidates, our financial position and results of operations would also be materially and adversely impacted.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- any of our AV-101 or other pending patent applications, if issued, will include claims having a scope sufficient to protect AV-101 or any other products or product candidates;
- any of our pending patent applications will issue as patents at all;
- we will be able to successfully commercialize our product candidates, if approved, before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe our patents;
- others will not use pre-existing technology to effectively compete against us;
- any of our patents, if issued, will be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;

- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- that our commercial activities or products will not infringe upon the patents or proprietary rights of others.

We rely upon unpatented trade secrets, unpatented know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. It is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants who are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could otherwise become known or be independently discovered by our competitors.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing our product candidates, if approved.

Our success will depend in part on our ability to operate without infringing the intellectual property and proprietary rights of third parties. We cannot assure you that our business, products and methods do not or will not infringe the patents or other intellectual property rights of third parties.

Table of Contents

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that our product candidates or the use of our technologies infringes patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. As we continue to develop and, if approved, commercialize our current product candidates and future product candidates, competitors may claim that our technology infringes their intellectual property rights as part of business strategies designed to impede our successful commercialization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, third parties may have currently pending patent applications which may later result in issued patents that our product candidates may infringe, or which such third parties claim are infringed by our technologies. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid, and we may not be able to do this. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on us. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. Any claim relating to intellectual property infringement that is successfully asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing our product candidates.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our products. Patent litigation is costly and time-consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, intellectual property litigation or claims could force us to do one or more of the following:

- cease developing, selling or otherwise commercializing our product candidates;
- pay substantial damages for past use of the asserted intellectual property;
- obtain a license from the holder of the asserted intellectual property, which license may not be available on reasonable terms, if at all; and
- in the case of trademark claims, redesign, or rename, some or all of our product candidates to avoid infringing the intellectual property rights of third parties, which may not be possible and, even if possible, could be costly and time-consuming.

Any of these risks coming to fruition could have a material adverse effect on our business, results of operations, financial condition and prospects.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We enter into confidentiality and intellectual property assignment agreements with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors. These agreements generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. For example, even if we have a consulting agreement in place with an academic advisor pursuant to which such academic advisor is required to assign any inventions developed in connection with providing services to us, such academic advisor may not have the right to assign such inventions to us, as it may conflict with his or her obligations to assign all such intellectual property to his or her employing institution.

Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The U.S. Patent and Trademark Office, or U.S. PTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

Table of Contents

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Even if the patent applications we own or license are issued, competitors may infringe these patents. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable and/or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent, if and when issued, covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review and equivalent proceedings in foreign jurisdictions, e.g., opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover our product candidates or competitive products. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

We will not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on product candidates in all countries and jurisdictions throughout the world is prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States, assuming that rights are obtained in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. The statutory deadlines for pursuing patent protection in individual foreign jurisdictions are based on the priority date of each of our patent applications. For the patent applications relating to AV-101, as well as for many of the patent families that we own or license, the relevant statutory deadlines have not yet expired. Thus, for each of the patent families that we believe provide coverage for our lead product candidates or technologies, we will need to decide whether and where to pursue protection outside the United States.

Competitors may use our technologies in jurisdictions where we do not pursue and obtain patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Even if we pursue and obtain issued patents in particular jurisdictions, our patent claims or other intellectual property rights may not be effective or sufficient to prevent third parties from so competing.

Table of Contents

The laws of some foreign countries do not protect intellectual property rights to the same extent as the laws of the United States. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, particularly developing countries, do not favor the enforcement of patents and other intellectual property protection, especially those relating to biotechnology. This could make it difficult for us to stop the infringement of our patents, if obtained, or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Furthermore, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We are dependent, in part, on licensed intellectual property. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing our product candidates, if approved. If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties or, in certain cases, we fail to meet certain development or payment deadlines, we could lose license rights that are important to our business.

We are a party to a number of license agreements under which we are granted rights to intellectual property that are or could become important to our business, and we expect that we may need to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose on us, various development, regulatory and/or commercial diligence obligations, payment of fees, milestones and/or royalties and other obligations. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to develop or market products which could be covered by the license. Our business could suffer, for example, if any current or future licenses terminate, if the licensors fail to abide by the terms of the license, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms. See “Business—Licenses” for a description of our license agreements, which includes a description of the termination provisions of these agreements.

As we have done previously, we may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we cannot provide any assurances that third-party patents do not exist that might be enforced against our current product candidates or future products in the absence of such a license. We may fail to obtain any of these licenses on commercially reasonable terms, if at all. Even if we are able to obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could materially harm our business and the third parties owning such intellectual property rights could seek either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties and/or other forms of compensation.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

Table of Contents

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We have entered into several licenses to support our various programs. We may enter into additional license(s) to third-party intellectual property that are necessary or useful to our business. Our current licenses and any future licenses that we may enter into impose various royalty payment, milestone, and other obligations on us. For example, the licensor may retain control over patent prosecution and maintenance under a license agreement, in which case, we may not be able to adequately influence patent prosecution or prevent inadvertent lapses of coverage due to failure to pay maintenance fees. If we fail to comply with any of our obligations under a current or future license agreement, our licensor(s) may allege that we have breached our license agreement and may accordingly seek to terminate our license with them. In addition, future licensor(s) may decide to terminate our license at will. Termination of any of our current or future licenses could result in our loss of the right to use the licensed intellectual property, which could materially adversely affect our ability to develop and commercialize a product candidate or product, if approved, as well as harm our competitive business position and our business prospects.

In addition, if our licensors fail to abide by the terms of the license, if the licensors fail to prevent infringement by third parties, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms our business could suffer.

If we do not take adequate steps to commercialize certain intellectual property rights, or certain exigent circumstances relating to public health and safety prescribed under U.S. law become applicable, the U.S. government may acquire certain rights with respect to intellectual property we have developed under federally funded research and development grants and contracts, including inventions related to AV-101, and, in those certain circumstances, which are prescribed under federal law, we could ultimately share or lose certain intellectual property rights.

Some of our intellectual property rights have been or may be developed in the course of research funded by the U.S. government, including patent applications relating to AV-101. As a result, under certain circumstances prescribed under federal law pursuant to the Bayh-Dole Act of 1980, the U.S. government may acquire certain rights to intellectual property embodied in our current or future products. Government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive licenses to any of these inventions to a third party if they determine that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations. The U.S. government also has the right to take title to these inventions if we fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. In addition, the U.S. government may acquire title in any country in which a patent application is not filed within specified time limits. If any of our intellectual property becomes subject to any of the rights or remedies available to the U.S. government or third parties pursuant to the Bayh-Dole Act of 1980, this could impair the value of our intellectual property and could adversely affect our business.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent terms and obtaining data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, one or more of the U.S. patents we own or license may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, 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, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. For example, we may not be granted an extension if the active ingredient of AV-101 is used in another drug company's product candidate and that product candidate is the first to obtain FDA approval. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our ability to generate revenues could be materially adversely affected.

Table of Contents

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore costly, time-consuming and inherently uncertain. In addition, the United States has recently enacted and is currently implementing wide-ranging patent reform legislation: the Leahy-Smith America Invents Act, referred to as the America Invents Act. The America Invents Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. It is not yet clear what, if any, impact the America Invents Act will have on the operation of our business. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of any patents that may issue from our patent applications, all of which could have a material adverse effect on our business and financial condition.

In addition, recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. The full impact of these decisions is not yet known. For example, on March 20, 2012 in *Mayo Collaborative Services, DBA Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, the Court held that several claims drawn to measuring drug metabolite levels from patient samples and correlating them to drug doses were not patentable subject matter. The decision appears to impact diagnostics patents that merely apply a law of nature via a series of routine steps and it has created uncertainty around the ability to obtain patent protection for certain inventions. Additionally, on June 13, 2013 in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the Court held that claims to isolated genomic DNA are not patentable, but claims to complementary DNA molecules are patent eligible because they are not a natural product. The effect of the decision on patents for other isolated natural products is uncertain. However, on March 4, 2014, the U.S. PTO issued a memorandum to patent examiners providing guidance for examining claims that recite laws of nature, natural phenomena or natural products under the *Myriad* and *Prometheus* decisions. This guidance did not limit the application of *Myriad* to DNA but, rather, applied the decision to other natural products.

In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on these and other decisions by the U.S. Congress, the federal courts and the U.S. PTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce any patents that may issue in the future.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Certain of our current employees have been, and certain of our future employees may have been, previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. We also engage advisors and consultants who are concurrently employed at universities or who perform services for other entities.

Although we are not aware of any claims currently pending or threatened against us, we may be subject to claims that we or our employees, advisors or consultants have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of a former employer or other third party. We have and may in the future also be subject to claims that an employee, advisor or consultant performed work for us that conflicts with that person's obligations to a third party, such as an employer, and thus, that the third party has an ownership interest in the intellectual property arising out of work performed for us. Litigation may be necessary to defend against

these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying monetary claims, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to commercialize our product candidates, which would materially adversely affect our commercial development efforts.

-29-

Table of Contents

Numerous factors may limit any potential competitive advantage provided by our intellectual property rights.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, provide a barrier to entry against our competitors or potential competitors, or permit us to maintain our competitive advantage. Moreover, if a third party has intellectual property rights that cover the practice of our technology, we may not be able to fully exercise or extract value from our intellectual property rights. The following examples are illustrative:

- others may be able to develop and/or practice technology that is similar to our technology or aspects of our technology but that is not covered by the claims of patents, should such patents issue from our patent applications;
- we might not have been the first to make the inventions covered by a pending patent application that we own;
- we might not have been the first to file patent applications covering an invention;
- others may independently develop similar or alternative technologies without infringing our intellectual property rights;
- pending patent applications that we own or license may not lead to issued patents;
- patents, if issued, that we own or license may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- third parties may compete with us in jurisdictions where we do not pursue and obtain patent protection;
- we may not be able to obtain and/or maintain necessary or useful licenses on reasonable terms or at all;
- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could significantly harm our business and results of operations.

If we seek to leverage prior discovery and development of drug rescue candidates under in-license arrangements with academic laboratories, biotechnology companies, the NIH, pharmaceutical companies or other third parties, it is uncertain what ownership rights, if any, we will obtain over intellectual property we derive from such licenses to drug rescue NCEs we may produce or develop in connection with any such third-party licenses.

If, instead of identifying drug rescue candidates based on information available to us in the public domain, we seek to in-license drug rescue candidates from biotechnology, medicinal chemistry and pharmaceutical companies, academic, governmental and nonprofit research institutions, including the NIH, or other third-parties, there can be no assurances that we will obtain material ownership or economic participation rights over intellectual property we may derive from such licenses or similar rights to the drug rescue NCEs we may produce and develop. If we are unable to obtain ownership or substantial economic participation rights over intellectual property related to drug rescue NCEs we produce and develop, our business may be adversely affected.

Risks Related to our Common Stock

There is no assurance that an active, liquid and orderly trading market will develop for our common stock or what the market price of our common stock will be and, as a result, it may be difficult for you to sell your shares of our common stock.

Since we became a publicly-traded company in May 2011, there has been a limited public market for shares of our common stock on the OTCQB Marketplace (“OTCQB”). We do not yet meet the initial listing standards of the New York Stock Exchange, the NASDAQ Capital Market, or other similar national securities exchanges. Until our common stock is listed on a broader exchange, we anticipate that it will remain quoted on the OTC Markets. In that venue, investors may find it difficult to obtain accurate quotations as to the market value of our common stock. In addition, if we fail to meet the criteria set forth in SEC regulations, various requirements would be imposed by law on broker-dealers who sell our securities to persons other than established customers and accredited investors. Consequently, such regulations may deter broker-dealers from recommending or selling our common stock, which may further affect liquidity. This could also make it more difficult to raise additional capital.

Table of Contents

We cannot predict the extent to which investor interest in our company will lead to the development of a more active trading market on the OTC Markets, whether we will meet the initial listing standards of the New York Stock Exchange, the NASDAQ Capital Market, or other similar national securities exchanges, or how liquid that market might become. If an active trading market does not develop, you may have difficulty selling any of the shares of our common stock that you buy.

Market volatility may affect our stock price and the value of your investment.

The market price for our common stock, similar to other biopharmaceutical companies, is likely to be volatile. The market price of our common stock may fluctuate significantly in response to a number of factors, most of which we cannot control, including, among others:

- plans for, progress of or results from non-clinical studies and clinical trials of our product candidates;
- the failure of the FDA to approve our product candidates;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of other CNS therapies;
- regulatory or legal developments in the United States and other countries;
- failure of our product candidates, if approved, to achieve commercial success;
- fluctuations in stock market prices and trading volumes of similar companies;
- general market conditions and overall fluctuations in U.S. equity markets;
- variations in our quarterly operating results;
- changes in our financial guidance or securities analysts' estimates of our financial performance;
- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders;
- additions or departures of key personnel;
- discussion of us or our stock price by the press and by online investor communities; and
- other risks and uncertainties described in these risk factors.

Future sales of our common stock may cause our stock price to decline.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur could significantly reduce the market price of our common stock and impair our ability to raise adequate capital through the sale of additional equity securities.

The stock market in general, and biotechnology-based companies like ours in particular, has from time to time experienced volatility in the market prices for securities that often has been unrelated to the operating performance of the underlying companies. These broad market and industry fluctuations may adversely affect the market price of our common stock, regardless of our operating performance. In certain recent situations in which the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against such company that issued the stock. If any of our stockholders were to bring a lawsuit against us, the defense and disposition of the lawsuit could be costly and divert the time and attention of our management and harm our operating results. Additionally, if the trading volume of our common stock remains low and limited there will be an increased level of volatility and you may not be able to generate a return on your investment.

Table of Contents

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future. Future sales of shares by existing stockholders could cause our stock price to decline, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Prior to this date of this prospectus, there has been a limited public market for shares of our common stock on the OTC Markets. Future sales of a substantial number of shares of our common stock in the public market, including shares issued upon the exchange of our Series A Preferred Stock, and Series B 10% Convertible Preferred Stock under this prospectus, and exercise of outstanding options and warrants for common stock, including shares of common stock under this prospectus which are issuable upon exercise of warrants, in the public market, or the perception that these sales might, occur, could significantly reduce the market price for our common stock and impair our ability to raise adequate capital through the sale of equity securities.

Our principal institutional stockholders may continue to have substantial control over us and could limit your ability to influence the outcome of key transactions, including changes in control.

Certain of our current institutional stockholders and their respective affiliates own a substantial portion of our outstanding capital stock, including our common stock, Series A Preferred Stock and Series B 10% Convertible Preferred Stock, which preferred stock is convertible into a substantial number of shares of common stock. Accordingly, these stockholders may exert significant influence over us and over the outcome of any corporate actions requiring approval of holders of our common stock, including the election of directors and amendments to our organizational documents, such as increases in our authorized shares of common stock, any merger, consolidation or sale of all or substantially all of our assets or any other significant corporate transactions. These stockholders may also delay or prevent a change of control of us, even if such a change of control would benefit our other stockholders. The significant concentration of stock ownership may adversely affect the trading price of our common stock due to investors' perception that conflicts of interest may exist or arise. Furthermore, the interests of our principal institutional stockholders may not always coincide with your interests or the interests of other stockholders may act in a manner that advances its best interests and not necessarily those of other stockholders, including seeking a premium value for its common stock, which might affect the prevailing market price for our common stock.

If equity research analysts do not publish research or reports about our business or if they issue unfavorable commentary or downgrade our common stock, the price of our common stock could decline.

The trading market for our common stock relies in part on the research and reports that equity research analysts publish about us and our business. We do not control these analysts. The price of our common stock could decline if one or more equity research analysts downgrade our common stock or if analysts issue other unfavorable commentary or cease publishing reports about us or our business.

There may be additional issuances of shares of preferred stock in the future.

Our Articles of Incorporation permit us to issue up to 10.0 million shares of preferred stock. Our Board of Directors has authorized the issuance of both 500,000 shares of Series A Preferred, all of which shares are currently issued and outstanding, and 4.0 million shares of Series B 10% Convertible Preferred Stock, of which approximately 3.5 million shares are issued and outstanding as of the date of this prospectus. Our Board of Directors could authorize the issuance of additional series of preferred stock in the future and such preferred stock could grant holders preferred rights to our assets upon liquidation, the right to receive dividends before dividends would be declared to holders of our common stock, and the right to the redemption of such shares, possibly together with a premium, prior to the redemption of the common stock. In the event and to the extent that we do issue additional preferred stock in the

future, the rights of holders of our common stock could be impaired thereby, including without limitation, with respect to liquidation.

We do not intend to pay dividends on our common stock and, consequently, your ability to achieve a return on your investment will depend on appreciation in the price of our common stock.

We have never declared or paid any cash dividend on our common stock and do not currently intend to do so in the foreseeable future. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends in the foreseeable future. Therefore, the success of an investment in shares of our common stock will depend upon any future appreciation in their value. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which you purchased them.

-32-

Table of Contents

USE OF PROCEEDS

We will not receive any of the proceeds of the shares of common stock which may be offered and resold by the Selling Stockholders from time-to-time under this prospectus. However, we may receive proceeds upon exercise of Warrants (discussed below). The shares of common stock that may be resold under this prospectus are issuable upon the conversion of certain securities issued by us in the Private Placements, or upon exercise of Warrants. The funds that may be received by us upon exercise of Warrants, estimated to be up to approximately \$7.2 million, if all Warrants are exercised, will be used for general working capital purposes.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus includes forward-looking statements that relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Words such as, but not limited to, “believe,” “expect,” “anticipate,” “estimate,” “intend,” “plan,” “targets,” “likely,” “will,” “would,” “could,” and similar expressions or phrases are used to identify forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our ability to implement our business strategy;
- anticipated trends and challenges in our business and the markets in which we operate;
- our expected future financial performance;
- our expectations regarding our operating expenses;
- our ability to anticipate market needs or develop new or enhanced products to meet those needs;
- our expectations regarding market acceptance of our products;
- our ability to compete in our industry and innovation by our competitors;
- our ability to protect our confidential information and intellectual property rights;
- our ability to obtain additional financing; and
- our ability to manage growth.

All forward-looking statements involve risks, assumptions and uncertainties. The occurrence of the events described, and the achievement of the expected results, depend on many events, some or all of which are not predictable or within our control. Actual results may differ materially from expected results. See the section titled “Risk Factors” and elsewhere in this prospectus for a more complete discussion of these risks, assumptions and uncertainties and for other risks and uncertainties. These risks, assumptions and uncertainties are not necessarily all of the important factors that could cause actual results to differ materially from those expressed in any of our forward-looking statements. Other unknown or unpredictable factors also could harm our results. In light of these risks, uncertainties and assumptions, the forward-looking events discussed in this prospectus might not occur.

Readers are cautioned not to place undue reliance on forward-looking statements, as there can be no assurance that the plans, intentions or expectations upon which they are based will occur. By their nature, forward-looking statements

involve numerous assumptions, known and unknown risks and uncertainties, both general and specific, that contribute to the possibility that the predictions, forecasts, projections and other things contemplated by the forward-looking statements will not occur. Forward-looking statements in this prospectus are based on management's beliefs and opinions at the time the statements are made. The forward-looking statements contained in this prospectus are expressly qualified in their entirety by this cautionary statement. The forward-looking statements included in this prospectus are made as of the date of this prospectus and we undertake no obligation to publicly update or revise any forward-looking statements to reflect new information, future events or otherwise, except as required by applicable securities laws.

Table of Contents

BUSINESS

Company Overview

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

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

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

Following two successful randomized, double-blind, placebo-controlled Phase 1 safety studies funded by the NIH, in February 2015, we entered into a Cooperative Research and Development Agreement (“CRADA”) with the U.S. National Institute of Mental Health (“NIMH”), part of the NIH. Under the CRADA, we will collaborate with the NIMH on the initial Phase 2 clinical study of AV-101 in subjects with treatment-resistant MDD. Pursuant to the CRADA, the study will be conducted at the NIMH and be fully funded by the NIMH. It is contemplated that this clinical study will begin in Fall 2015 under the direction of Dr. Carlos Zarate, Jr., the NIMH’s Chief of Experimental Therapeutics & Pathophysiology Branch and of the Section on Neurobiology and Treatment of Mood and Anxiety Disorders.

In addition to developing AV-101 for MDD and other CNS indications, we apply our stem cell technology for drug rescue programs intended to identify and develop proprietary new chemical entities (“NCEs”) for our internal drug candidate pipeline. Drug rescue involves (1) using our customized in vitro bioassay systems to predict potential heart and liver toxicity of NCEs, (2) leveraging prior investments by pharmaceutical companies and others related to screening large-scale compound libraries, optimizing and testing for efficacy NCEs that were terminated before FDA approval due to heart or liver toxicity and are now available in the public domain, and (3) applying modern medicinal chemistry to produce safer NCEs for our internal development pipeline. Our CardioSafe 3D™ bioassay system uses our human pluripotent stem cell (“hPSC”)–derived cardiomyocytes, or human heart cells. We believe CardioSafe 3D is more comprehensive and clinically predictive than the hERG assay, which is currently the only in vitro cardiac safety assay required by FDA guidelines. We use our hPSC-derived hepatocytes, or human liver cells, in our LiverSafe 3D™ bioassay system to predict potential liver toxicity of NCEs, including potential drug metabolism issues and adverse drug-drug interactions. CardioSafe 3D and LiverSafe 3D offer a new paradigm for evaluating and predicting potential heart and liver toxicity of NCEs, including drug rescue NCEs, early in the development process, long before costly, high risk animal studies and human clinical trials. We intend to develop internally for our pipeline each lead drug

rescue NCEs we produce.

-34-

Table of Contents

Our Strategy

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

- Develop and commercialize our lead product candidate, AV-101, for depression, including MDD. We are pursuing MDD as our lead indication for AV-101. We are preparing to launch our initial MDD Phase 2 clinical study in collaboration with the NIH in the second half of 2015. We intend to develop AV-101 internally, through Phase 3 clinical studies and submission of our NDA. If approved by the FDA, we plan to commercialize AV-101 for this indication in the U.S. either by (A) establishing or contracting for a specialty U.S. sales force focused primarily on psychiatrists and long-term care physicians who are high prescribers of currently-approved antidepressants or (B) collaborating with a pharmaceutical company with an extensive presence in U.S. CNS markets. Outside the U.S., we may choose to commercialize AV-101 in selected markets by establishing one or more strategic alliances.
- Leverage the commercial potential AV-101 by expanding to additional CNS-related disorders. We intend to pursue the development and commercialization of AV-101 in MDD and additional CNS-related indications that are underserved by currently available medicines and represent large unmet medical needs. Based on AV-101 preclinical studies, and by leveraging our AV-101 IND and successful Phase 1 clinical studies, we now have the opportunity to explore Phase 2 development of AV-101 as a potential treatment for chronic neuropathic pain, epilepsy and neurodegenerative diseases such as Parkinson's disease and Huntington's disease.
- Grow our internal development pipeline by pursuing drug rescue opportunities using our stem cell technology. We are using our stem cell technology to screen and develop proprietary new chemical entities ("NCEs") through drug rescue programs intended to produce proprietary NCEs for our internal drug development pipeline. We will focus on NCEs with established therapeutic and commercial potential. Our ability to build on that valuable head start with our biological and electrophysiological insights regarding cardiac and liver safety effects of NCEs obtained using CardioSafe 3D and, eventually, LiverSafe 3D, we believe will help us produce and then optimize patentable drug rescue NCEs for our internal pipeline without incurring many of the substantial costs and risks typically inherent in new drug discovery and nonclinical drug development.
- Pursue other product candidates, including product candidates for treatment of CNS-related disorders. While our resources are currently focused on developing AV-101 and producing drug rescue NCEs, we may pursue additional product candidates in the future. These may be directed at CNS-related disorders and may be developed independently or in partnerships. We believe that a diversified portfolio will mitigate risks inherent in drug development and increase the

likelihood of our success.

Our Product Opportunities

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

Overview and Mechanism of Action

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

-35-

Table of Contents

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

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

Major Depressive Disorder

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

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

Current Antidepressants

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

Ketamine and NIH Clinical Studies in Major Depressive Disorder

Ketamine hydrochloride ("ketamine") is an FDA-approved, rapid-acting general anesthetic. The use of ketamine (an NMDA receptor antagonist which acts as an NMDA channel blocker) to treat MDD has been studied in several clinical trials conducted by depression experts at the U.S. National Institute of Mental Health ("NIMH"), part of the NIH, including Dr. Carlos Zarate, Jr., the NIMH's Chief of Experimental Therapeutics & Pathophysiology Branch and of the Section on Neurobiology and Treatment of Mood and Anxiety Disorders. In randomized, placebo-controlled, double-blind clinical trials reported by Dr. Zarate and others at the NIMH, a single intravenous dose of ketamine (0.5

mg/kg over 40 minutes) produced robust and rapid antidepressant effects in MDD patients who had not responded to currently-approved medications. These results were in contrast to the slow onset of currently FDA-approved antidepressant medications, which usually require many weeks or months of chronic usage to achieve similar antidepressant effects. The potential for widespread therapeutic use of ketamine, and FDA Schedule III drug, is limited by its potential for abuse, dissociative and psychosis-like side effects, and by practical challenges associated with its intravenous administration in a medical center. Notwithstanding these limitations, the discovery of ketamine's fast-acting antidepressant effects revolutionized thinking about the MDD treatment paradigm. The discovery also increased interest in the development of a new generation of antidepressants with a fast-acting mechanism of action similar to ketamine's. Our orally available AV-101 is among the new generation of antidepressants with potential to deliver ketamine-like antidepressant effects, without ketamine's side effects or required intravenous administration.

Table of Contents

AV-101 and Major Depressive Disorder

AV-101 is an orally available prodrug candidate that produces, in the brain, 7 CI 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 different from currently available antidepressants, placing it among a new generation of glutamatergic antidepressants with potential to treat millions of MDD sufferers worldwide who are poorly served by SSRIs, SNRIs and other current depression therapies. AV-101 is functionally similar to ketamine in that both are NMDAR antagonists. However, AV-101 modulates (down-regulated) NMDAR channel activity and ketamine blocks it. AV-101 accomplishes this NMDAR modulation by selectively binding to the functionally required GlyB site of the NMDAR, thus down-regulating the NMDAR in a dose-dependent manner. We believe targeting the GlyB site of the NMDAR and modulating NMDAR activity rather than blocking it can bypass adverse effects that result when ketamine blocks the NMDA ion channel, without affecting the robust efficacy observed in previous clinical studies conducted by the NIH and others using ketamine to treat MDD. This NMDAR modulation by AV-101 may then result in the "glutamate surge," and the increase in neuronal connections, that has been associated with the fast-acting antidepressant effects of ketamine.

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

Building on over \$8.8 million of prior non-dilutive funding from the NIH for preclinical and Phase 1 clinical development of AV-101, in February 2015, we entered a Cooperative Research and Development Agreement ("CRADA") with the NIMH. Under the CRADA, we will collaborate with Dr. Carlos Zarate and the NIMH on a Phase 2 clinical study of AV-101 in subjects with treatment-resistant MDD. Pursuant to the CRADA, this study will be conducted at the NIMH by Dr. Zarate and fully-funded by the NIH. The primary objective of the NIH-sponsored Phase 2 study will be to evaluate the ability of AV-101 to improve overall depressive symptomatology in subjects with MDD, specifically whether subjects with MDD have a greater and more rapid decrease in depressive symptoms when treated with AV-101 than with placebo. We currently anticipate commencement of the study in the second half of 2015.

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

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

Chronic Neuropathic Pain and Acute Tissue Injury Hyperalgesia

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

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

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

-37-

Table of Contents

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

Epilepsy

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

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

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

1. AV-101 is preferentially converted to 7-Cl-KYNA in brain areas related to neuronal injury. This is because astrocytes, which are responsible for the enzymatic transamination of 4-Cl-KYN prodrug to active 7-Cl-KYNA, are focally activated at sites of neuronal injury. Due to AV-101's highly focused site of conversion, local concentrations of newly formed 7-Cl-KYNA are greatest at the site of therapeutic need. In addition to delivering the drug where it is needed, this reduces the chance of systemic and dangerous side effects with long-term use of the drug; and
2. An active metabolite of AV-101, 4-Cl-3-hydroxyanthranilic acid, inhibits the synthesis of quinolinic acid, an endogenous NMDAR agonist that causes convulsions and excitotoxic neuronal damage.

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

Parkinson's Disease

AV-101 has been shown to activate ventral tegmental area ("VTA") dopaminergic ("DA") neurons. Kynurenic acid ("KYNA") is an endogenous NMDA receptor antagonist, as well as a blocker of the 7-nicotinic acid receptor. Mounting

evidence suggests that this compound participates in the pathophysiology of schizophrenia. Preclinical studies have shown that elevated levels of endogenous KYNA are associated with increased firing of midbrain DA neurons. AV-101 is converted to the selective NMDAR GlyB antagonist 7-Cl-KYNA, which is 20 times more potent and selective than KYNA in binding the GlyB site. Utilizing extra cellular single unit cell recording techniques, we have shown that AV-101, which is converted to the selective NMDAR GlyB antagonist 7-Cl-KYNA, significantly increases the firing rate and percent burst firing activity of VTA DA neurons. These results have potential therapeutic implications for Parkinson's disease.

-38-

Table of Contents

Huntington's Disease

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

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

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

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

Summary of Additional AV-101 Nonclinical Information

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

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

Oral administration of AV-101 to Sprague-Dawley rats and mice was shown to result in rapid absorption of AV-101 (rats: time to maximum plasma concentration [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-Cl-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-Cl-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-Cl-KYN during these hepatocyte incubations was noted. Results from cytochrome P-450 (“CYP”) inhibition and induction studies showed that AV-101 was not a potent inhibitor or inducer of the human CYP isoforms evaluated.

Table of Contents

Single-dose studies in rats and monkeys did not show clear 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.

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

Nonclinical Pharmacology Studies

Primary Pharmacodynamics

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

Nonclinical Absorption, Distribution, Metabolism and Excretion Studies

In rats, area under the concentration-time curve from time of dosing extrapolated to infinity ($AUC_{0-\infty}$) 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, L-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 L-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, L-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-∞} 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-∞} estimates were also generally higher in females relative to males at all dose levels. No clear sex differences were noted for L-4-Cl-KYN.

In monkeys, AUC_{0-∞} 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-∞} 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 were determined to be mutagenic.

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

The results of the pivotal 14-day studies show the dog to be the most sensitive species. The dog NOAEL was determined to be the highest dose level (120 mg/kg/d), and therefore the maximum recommended starting dose (MRSD) would be 6.5 mg/kg (12 mg/kg/d × 0.54 [conversion factor]) or 390 mg per subject for a 60-kg person. As a further added margin of safety for the clinical use of AV-101, VistaGen applied an additional safety factor to the calculated MRSD, and set the starting dose in the proposed Phase 1a clinical trial at 0.5 mg/kg (i.e., 30 mg for 60 kg subjects).

Table of Contents

Summary of AV-101 Phase 1 Clinical Safety Studies

The safety data from two NIH-funded AV-101 Phase 1 clinical safety studies indicate that AV-101 was safe and well-tolerated at all three doses tested. Overall, 57 mild to moderate AEs were reported by 34 subjects, with 17 AEs (29.8%) occurring in the placebo group. There was a higher rate of AEs reported from subjects that received placebo than from subjects that received AV-101. A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo. Additionally, 49 of the 57 total AEs (85.9%) were considered mild, and the remaining 8 AEs (14.0%) were considered moderate. Of these AEs, headache was the most commonly reported preferred term. All of the AEs were completely resolved.

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

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

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/57) of the subjects receiving AV-101 and 0% of the 31 subjects receiving placebo reported “feelings of well-being” (coded as euphoric mood), similar to the fast-acting antidepressant effects reported in the literature with ketamine.

Phase 1 Clinical Safety Trials

Phase 1a Study (VSG-CL-101)

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 L-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 at the 1,440-mg cohort, and the study was stopped and did not proceed to the planned 1,800 mg cohort.

Phase 1a Study Pharmacokinetics Summary

Validated bioanalytical methods were used to measure plasma analyte concentrations. These assays had lower limits of quantification of 2 ng/mL for 7-Cl-KYNA and 5 ng/mL for L-4-Cl-KYN and D-4-Cl-KYN. Pharmacokinetic parameters were calculated by using WinNonlin Pro v. 5.2. Parameters calculated included observed maximal concentration (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 (AV-101) and 7-Cl-KYNA were obtained in addition to urine concentrations of these two analytes. Plasma and urine concentrations of D-4-Cl-KYN also were determined, but will be reported only for the first two cohorts.

This study was conducted under dose escalation stopping criteria as determined by the FDA of 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.

Table of Contents

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.

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 AUC₀₋ 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.

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

Table of Contents

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

Assessment of Dose Proportionality

For 4-Cl-KYN, mean C_{max} and AUC₀₋ values appeared to be approximately dose proportional except for those of the highest dose group. These values are presented by dose in Figure 3 (C_{max}) and in Figure 4 (AUC₀₋) 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, AUC₀₋ 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 AUC₀₋ values were linear throughout the dose range suggests that the extent of absorption was not a limitation, but the rate of absorption may be limited at doses above 1,080 mg.

Table of Contents

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 (AUC₀₋).

Figure 3. Mean C_{max} values of 4-Cl-KYN by dose of AV-101.

Figure 4. Mean AUC₀₋ values of 4-Cl-KYN by dose of AV-101.

Table of Contents

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

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

Phase 1a Safety Summary

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

Table of Contents

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

Table 1. Summary of Adverse Events, Phase 1a

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

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

Phase 1b Study (VSG-CL-102)

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

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

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

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

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

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

-46-

Table of Contents

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.

Table 2. Summary of Adverse Events, Phase-1b

	Dose Cohorts			
	360 mg AV-101 (N = 12) [n (%)]	1,080 mg AV-101 (N = 13) [n (%)]	1,440 mg AV-101 (N = 12) [n (%)]	Pooled Placebo (N = 13) [n (%)]
Number of AEs	16	14	10	17
Number of subjects with any AE	9 (75.0%)	8 (61.5%)	7 (58.3%)	10 (76.9%)
Number of SAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of AEs resulting in death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of AEs leading to discontinuation of study drug	0 (0%)	0 (0%)	0 (0%)	1 (7.7%)

AE = adverse event; SAE = serious adverse event.

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 blinded. 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 severe AEs were reported.

Even though these safety studies were not designed to quantitatively assess effects on mood, during the interviews certain subjects who received 360, 1080, and 1440 mg of AV-101, voluntarily acknowledged positive effects on

mood. Similar comments were not made by any of the placebo-group subjects.

Phase 1b 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}.

-47-

Table of Contents

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 AUC₀₋ 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 AUC₀₋ 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. $\geq 31\%$.

In conclusion, 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 - Overall Safety Conclusions

The Phase 1a and Phase 1b safety data indicate that AV-101 was safe and well tolerated at all three doses tested. Overall, 57 AEs were reported by 34 subjects, with 17 AEs (29.8%) occurring in the placebo group. There was a higher rate of AEs reported from subjects that received placebo than from subjects that received AV-101. A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo. Additionally, 49 of the 57 total AEs (85.9%) were considered mild, and the remaining 8 AEs (14.0%) were considered moderate. Of these AEs, headache (nervous system disorder) was the most commonly reported preferred term. All of the AEs were completely resolved.

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

A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo (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.

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/57) of the healthy volunteer subjects receiving AV-101 and

0% of the 31 subjects receiving placebo reported “feelings of wellbeing” (coded as euphoric mood), similar to the rapid-onset antidepressant effects reported in the literature with ketamine. Table 3 lists the percent of adverse events reported by the subjects in each of the two Phase 1 studies and the number of events reported as euphoric mood per number of subjects on placebo and AV-101.

Table 1. Reports of Well-Being (coded as Euphoric Mood) in Phase 1 Clinical Studies

	Placebo % of Adverse Events/N	AV-101 % of Adverse Events/N
Phase 1a		
· Nonserious Adverse Events	22% (4/18)	28% (5/18)
· Feelings of Well-being (coded as euphoric mood)	0% (0/18)	11% (2/18)
Phase 1b		
· Nonserious Adverse Events	77% (10/13)	65% (24/37)
· Feelings of Well-being (coded as euphoric mood)	0% (0/13)	8% (3/37)
Phase 1a and 1b (combined)		
· Feelings of Well-being (coded as euphoric mood)	0% (0/31)	9% (5/55)

N = number of subjects

Table of Contents

The five events of feeling of well-being (coded as euphoric mood) occurred in one subject each at 360 (7%, 1 of 15 subjects) and 1,080 mg (6%, 1 of 16 subjects), and three subjects at 1,440 mg (20%, 3 of 15 subjects) in the Phase 1a and Phase 1b clinical studies. Four of the five subjects reporting well-being/euphoric mood 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

We believe better cells lead to better medicines™ and that the key to making better cells is precisely controlling the differentiation of human pluripotent stem cells (“hPSCs”), which are the building blocks of all cells of the human body. Our stem cell technology platform is based on proprietary and licensed technologies for controlling the differentiation of hPSCs and producing the multiple types of mature, non-transformed, functional, adult human cells that we use, or plan to use, to reproduce complex human biology and disease and assess, in vitro, the potential therapeutic benefits and safety risks of new chemical entities (“NCEs”).

We have used our hPSC-derived cardiomyocytes (human heart cells we refer to as VSTA-CMs™) to design and develop CardioSafe 3D™, our novel, customized in vitro bioassay system for predicting potential cardiotoxicity of NCEs, including drug rescue NCEs. We believe CardioSafe 3D is more comprehensive and clinically predictive than the hERG assay, currently the only in vitro cardiac safety assay required by FDA guidelines. We use our stem cell-derived hepatocytes (human liver cells we refer to as VSTA-heps™) as the foundation of LiverSafe 3D™, our second novel, customized bioassay system for predicting potential liver toxicity of new drug candidates, including potential drug metabolism issues and adverse drug-drug interactions. VSTA-heps are highly-functional, non-transformed, and have the majority of the functional properties of mature human hepatocytes. We believe our VSTA-heps have more functionally useful life-span in culture, and overcome numerous problems related to commercially-available primary (cadaver) hepatocytes currently used in FDA-required in vitro hepatocyte assays for drug metabolism. These commercially-available primary hepatocytes are generally in limited supply and the health status and genetic differences of the donor are unknown. We believe our VSTA-CMs, VSTA-heps, CardioSafe 3D and LiverSafe 3D offer a new paradigm for evaluating and predicting potential heart and liver toxicity of NCEs, including drug rescue NCEs, early in development, long before costly, high risk human clinical trials.

Scientific Background

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.

Human pluripotent stem cells (“hPSCs”) 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, including heart and liver biology for drug rescue.

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. We use multiple types of these mature cells as the foundation of 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 regenerative medicine applications.

Human Embryonic Stem Cells

According to the NIH, hESCs are derived from excess embryos that develop from eggs that have been fertilized in an in vitro fertilization (“IVF”) clinic and then donated for research purposes with the informed consent of the parental donors after a successful IVF procedure. Human embryonic stem cells are not derived from eggs fertilized in a woman’s body. Human ESCs are isolated when the embryo is approximately 100 cells, well before organs, tissues or nerves have developed.

Table of Contents

Human ESCs have the potential to both self-renew and differentiate. They undergo increasingly tissue-restrictive developmental decisions during their differentiation. These “fate decisions” commit the hESCs to becoming only a certain type of mature, functional cells and ultimately tissues. At one of the first fate decision points, hESCs differentiate into epiblasts. Although epiblasts cannot self-renew, they can differentiate into the major tissues of the body. This epiblast stage can be used, for example, as the starting population of cells that develop into millions of blood, heart, muscle, liver and insulin-producing pancreatic beta-islet cells, as well as neurons. In the next step, the presence or absence of certain growth factors, together with the differentiation signals resulting from the physical attributes of the cell culture techniques, induce the epiblasts to differentiate into neuroectoderm or mesendoderm cells. Neuroectoderm cells are committed to developing into cells of the skin and nervous systems. Mesendoderm cells are precursor cells that differentiate into mesoderm and endoderm. Mesoderm cells develop into muscle, bone and blood, among other cell types. Endoderm cells develop into the internal organs such as the heart, liver, pancreas and intestines, among other cell types.

Induced Pluripotent Stem Cells

It is also possible to obtain hPSC lines from individuals without the use of embryos. Induced PSCs are adult cells, typically human skin or fat cells that have been genetically reprogrammed to behave like hESCs by being forced to express genes necessary for maintaining the pluripotential properties of hESCs. Although researchers are exploring non-viral methods, most early iPSCs were produced by using various viruses to express three or four genes required for the immature pluripotential property similar to hESCs. It is not yet precisely known, however, how each gene actually functions to induce cellular pluripotency, nor whether each of the three or four genes is essential for this reprogramming. Although hESCs and iPSCs are believed to be similar in many respects, including their pluripotential ability to form all cells in the body and to self-renew, scientists do not yet know whether they differ in clinically significant ways or have the same ability to self-renew.

We believe the biology and differentiation capabilities of hESCs and iPSCs are likely to be comparable for most if not all purposes. There are, however, specific situations in which we may prefer to use one or the other type of hPSC. For example, we may prefer to use iPSCs for potential drug discovery applications based on the relative ease of generating iPSCs from:

- individuals with specific inheritable diseases and conditions that predispose the individual to respond differently to drugs; or
- individuals with specific variations in genes that directly affect drug levels in the body or alter the manner or efficiency of their metabolism, breakdown and/or elimination of drugs.