VistaGen Therapeutics, Inc.
Form S-1/A
May 10, 2016

As filed with the Securities and Exchange Commission on May 9, 2016

Registration No. 333-210152

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM S-1/A
(Amendment No. 3)

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

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

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

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

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

Copies of all communications to:

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

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

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

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

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

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

CALCULATION OF REGISTRATION FEE

Title Of Each Class Of Securities To Be Registered	Proposed Maximum Aggregate Offering Price (1)	Amount Of Registration Fee
Common stock, $0.001 par value (1)	$ 11,500,000	$ 1,158.05
Warrants to purchase shares of common stock (1) (2)	$ 115,000	$ 11.58
Shares of common stock issuable upon exercise of warrants (1)(3)(4)	$ 14,375,000	$ 1,447.56
Total	$ 25,990,000	$ 2,617.19 (5)

(1) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended (Securities Act). Includes offering price of securities that the underwriters have the option to purchase to cover over-allotments, if any.

(2) No fee pursuant to Rule 457(g) under the Securities Act.

(3) Estimated solely for purposes of calculating the registration fee pursuant to Rule 457(g) under the Securities Act.

(4) Pursuant to Rule 416, there is also being registered such indeterminable additional securities as may be issued to prevent dilution as a result of stock splits, stock dividends or similar transactions.

(5) Previously paid by the Registrant.

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

The information contained herein is subject to completion or amendment. A registration statement relating to these securities has been filed with the U.S. Securities and Exchange Commission. These securities may not be sold until the registration statement becomes effective. This preliminary prospectus is not an offer to sell and is not a solicitation of an offer to buy in any jurisdiction in which an offer, solicitation, or sale is not permitted.

PRELIMINARY PROSPECTUS SUBJECT TO COMPLETION DATED MAY 9, 2016

2,352,942 Shares of Common Stock

and

Warrants to Purchase up to 2,352,942 Shares of Common Stock

VistaGen Therapeutics, Inc. is offering 2,352,942 shares of common stock and warrants to purchase up to 2,352,942 shares of our common stock to purchasers in this offering (the Offering). Each share of common stock will be sold at a price of $[___] per share, and will be accompanied by a warrant to purchase one share of common stock for $[____] per share (125% of the public offering price of our common stock) at a price of $0.01 per warrant. The common stock and warrants are immediately separable but can only be purchased together in this Offering. The warrants are exercisable immediately and expire five years from the date of issuance.

Currently, our common stock is quoted for trading on the OTC Markets (OTCQB) under the symbol “VSTA.” We have applied for listing of our common stock on the NASDAQ Capital Market under the symbol “VTGN.” Although we believe we will satisfy NASDAQ Capital Market listing requirements, no assurance can be given that such listing will be achieved in a timely manner or at all. There is no established public trading market for the warrants, and we do not intend to apply to list the warrants on any securities exchange or automated quotation system.

On May 6, 2016, the closing price for our common stock, as quoted on the OTCQB, was $7.00 per share. Quotes on the OTCQB may not be indicative of the market price of our common stock on a national securities exchange, including the NASDAQ Capital Market.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should review carefully the risks and uncertainties described under the heading “Risk Factors” beginning on page 6 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 accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

	Per share	Per warrant	Total
Public offering price	$	$	$
Underwriting discounts and commissions (1)	$	$	$
Offering proceeds, before expenses	$	$	$

(1) We have agreed to reimburse the underwriters for certain expenses and the underwriters will receive compensation in addition to underwriting discounts and commissions. See the section titled “Underwriting” for additional disclosure regarding underwriter compensation and offering expenses.

We granted the underwriters a 45-day option the right to purchase an additional 352,942 shares of common stock and/or warrants to purchase up to an additional 352,942 shares of common stock from us at the offering price, less the underwriting discounts and commissions, to cover over-allotments, if any.

The underwriters expect to deliver the shares of common stock and warrants to purchasers on or about [__], 2016.

Joint Book-Running Managers

Chardan WallachBeth Capital, LLC

The date of this prospectus is [__], 2016

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ABOUT THIS PROSPECTUS

You should rely only on the information contained in this prospectus. We and the underwriters have not authorized anyone to provide any information or to make any representations other than those contained in this prospectus or in any free writing prospectuses we have prepared. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may provide you. We are offering to sell, and seeking offers to buy, our securities only in jurisdictions where offers and sales are permitted. 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 of any sale of our securities.

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

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

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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 such 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 (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 of 1933, as amended (Securities Act). Actual results could differ materially from those anticipated in forward-looking statements and future results could differ materially from historical performance.

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PROSPECTUS SUMMARY

This summary highlights selected information appearing elsewhere in this prospectus and does not contain all the information you should consider before investing in our common stock. You should carefully read this prospectus in its entirety before investing in our common stock, including the section entitled "Risk Factors" and our financial statements and related notes included elsewhere in this prospectus.

Overview

We are a clinical-stage biopharmaceutical company dedicated to developing and commercializing innovative product candidates for patients with diseases and disorders involving the central nervous system (CNS). Our lead product candidate, AV-101, is a next generation, orally available prodrug candidate in Phase 2 development, initially for the adjunctive treatment of Major Depressive Disorder (MDD) in patients with an inadequate response to standard antidepressants.

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

Our ongoing Phase 2a clinical study of AV-101 in subjects with treatment-resistant MDD is being conducted and funded by the U.S. National Institutes of Mental Health (NIMH) under our February 2015 Cooperative Research and Development Agreement (CRADA) with the NIMH. The first patient in this NIMH-sponsored Phase 2a study was dosed in November 2015. We anticipate results from this study in the second quarter of 2017. The Principal Investigator of the study is Dr. Carlos Zarate, Jr., Chief of the NIMH's Experimental Therapeutics & Pathophysiology Branch and its Section on Neurobiology and Treatment of Mood and Anxiety Disorders. Previous NIMH studies, including studies conducted by Dr. Zarate, have focused on the rapid onset antidepressant effects of intravenous (I.V.) ketamine in adult patients with treatment resistant MDD. These NIMH studies, as well as clinical research by others, have demonstrated robust antidepressant effects in patients with treatment-resistant MDD within hours of a single low dose of I.V. ketamine and stimulated research and development around a new generation of antidepressants, including AV-101, with potential to deliver ketamine-like fast-onset antidepressant benefits without its dissociative and other side effects. AV-101 is similar to ketamine because it acts on NMDA receptors. AV-101 is substantially safer than ketamine, however, because ketamine blocks the ion channel of NMDA receptors and AV-101 down-regulates NMDA receptors through the GlyB site.

Currently, we are preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. We anticipate commencement of this potentially pivotal, multi-center, multi-dose, double blind, placebo-controlled Phase 2b efficacy and safety study in the fourth quarter of 2016. Dr. Maurizio Fava, Professor of Psychiatry at Harvard Medical School and Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute and Executive Director, MGH Clinical Trials Network and Institute, will be the Principal Investigator of our Phase 2b study.

We also believe AV-101 has broad therapeutic utility with multiple near term CNS pipeline expansion opportunities, including chronic neuropathic pain, epilepsy, Huntington's disease and Parkinson's disease.

In addition to clinical development of AV-101, we are also focused on establishing strategic collaborations to advance potential commercial applications of our human pluripotent stem cell (hPSC) technology platform, including drug rescue to develop proprietary new chemical entities (NCEs) for our internal drug candidate pipeline, and regenerative medicine (RM) using blood, cartilage, heart and liver cells derived from our hPSC technology.

AV-101 and Major Depressive Disorder

Background

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

Most standard blockbuster antidepressants target neurotransmitter reuptake inhibition - serotonin (SSRIs) or serotonin/norepinephrine (SNRIs). Even when effective, standard antidepressants take many weeks to achieve adequate therapeutic benefits. Nearly two out of every three drug-treated depression patients obtain no benefit from initial treatment using standard antidepressants and have significant side effects, including anxiety, metabolic syndrome, sleep disturbance and sexual dysfunction. All standard antidepressants have a “Black Box” warning due to safety risks, including, in certain groups, worsening depression and risk of suicide. Unfortunately, even after treatment with as many as four different standard antidepressants, nearly one out of every three drug-treated depression patients do not achieve an adequate therapeutic response. These patients often transition to using atypical antipsychotics to augment their use of standard antidepressants. However, adjunctive use of atypical antipsychotics increases risk of serious side effects, including tardive dyskinesia, significant weight gain, diabetes and heart disease, while offering only a modest (10% to 20%) potential increase in therapeutic benefit.

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AV-101

AV-101, our orally available prodrug candidate, is in Phase 2 clinical development for the adjunctive treatment of MDD patients with an inadequate response to standard antidepressants. As published in the October 2015 issue of the peer-reviewed, Journal of Pharmacology and Experimental Therapeutics, in an article entitled, The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition, using well-established preclinical models of depression, AV-101 was shown to induce fast-acting, dose-dependent, persistent and statistically significant antidepressant-like responses, following a single treatment. These responses were equivalent to those seen with a single, sub-anesthetic control dose of the NMDAR antagonist ketamine. In the same preclinical studies, the SSRI fluoxetine did not induce rapid onset antidepressant-like responses.

Following the completion of our randomized, double blind, placebo-controlled Phase 1a and Phase 1b safety studies funded by the NIH, we are now collaborating with the NIMH under our February 2015 CRADA. Pursuant to the CRADA, the NIMH is sponsoring our ongoing Phase 2a efficacy and safety study of AV-101 in subjects with treatment-resistant MDD. The first patient in this study was dosed in November 2015. The trial is expected to enroll 24 to 28 patients, and results are expected in the second quarter of 2017. The Principal Investigator of this NIMH-sponsored Phase 2a study is Dr. Carlos Zarate, Jr. We are now preparing to launch our potentially pivotal Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants in the fourth quarter of 2016. This study is expected to enroll approximately 315 patients. The Principal Investigator of this potentially pivotal AV-101 Phase 2b MDD study will be Dr. Maurizio Fava of Harvard Medical School.

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

CardioSafe 3D™; NCE Drug Rescue and Regenerative Medicine

CardioSafe 3D™ is our customized in vitro cardiac bioassay system capable of predicting potential human heart toxicity of NCEs in vitro, long before they are ever tested in animal and human studies. Our current strategic interests involving CardioSafe 3D and our stem cell technology platform include collaborative arrangements focused on both (i) drug rescue designed to leverage substantial prior investments by pharmaceutical companies and others related to screening large-scale compound libraries, and optimizing and testing for efficacy NCEs terminated before FDA approval due to heart toxicity risks and now available in the public domain and (ii) nonclinical proof of concept studies to explore potential commercial RM applications involving hPSC-derived blood, bone, cartilage, heart and liver cells.

Risk Factors

Our business is subject to substantial risk. Please carefully consider the “Risk Factors” beginning on page 6 of this prospectus for a discussion of the factors you should carefully consider before deciding to purchase the securities offered by this prospectus. These risks include, among others:

- 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, which makes it difficult to assess our future viability;

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

failures or delays in the commencement or completion of our planned clinical trials could delay, prevent or limit our ability to generate revenue and continue our business;

we face significant competition, and if we are unable to compete effectively, we may not be able to achieve or maintain significant market penetration or improve our results of operations;

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

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; and

we have incurred significant net losses since inception and we will continue to incur substantial operating losses for the foreseeable future.

Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations. You should be able to bear a complete loss of your investment.

Corporate information

VistaGen Therapeutics, Inc., a Nevada corporation, is the parent of VistaGen Therapeutics, Inc., a California corporation founded in 1998. Our principal executive offices are located at 343 Allerton Avenue, South San Francisco, California 94080, and our telephone number is (650) 577-3600. Our website address is www.vistagen.com. The information contained on our website is not part of this prospectus. We have included our website address as a factual reference and do not intend it to be an active link to our website.

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THE OFFERING

Common stock offered by us	2,352,942 shares of common stock.
Warrants offered by us	Each share of common stock sold in this Offering will be accompanied by a warrant to purchase one share of our common stock, at a price of $[____] per share (125% of the public offering price of our common stock). The warrants will be immediately exercisable, and may be exercised for a period of five years following the date of issuance.
Common stock outstanding prior to Offering	2,525,276 shares (as of May 6, 2016).
Over-allotment option	The underwriters have an option for a period of 45 days to purchase up to 352,942 additional shares of common stock and/or warrants to purchase up to 352,942 additional shares of common stock from us at the public offering price, less underwriting discounts and commissions solely to cover over-allotments.
Common stock outstanding after the Offering	7,620,293 shares (assuming no exercise of any of the warrants offered hereby), or 9,973,293 shares if the warrants offered hereby are exercised in full.
Use of proceeds	We estimate that net proceeds to us from this Offering will be approximately $[___] million, or approximately $[___] million if the underwriters exercise their option to purchase additional shares and/or warrants in full, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. We currently intend to use the net proceeds from this Offering for research and development, working capital needs, capital expenditures and other general corporate purposes. See “Use of Proceeds” for additional information regarding the intended use of proceeds from the Offering.
Dividend policy	We have never declared or paid and do not anticipate declaring or paying any cash dividends on our common stock in the near future. You should read the “Dividend Policy” section of this prospectus

	for more information on future declarations and payments of dividends.
OTCQB common stock symbol	VSTA.
NASDAQ application	We have applied to have our common stock listed on The NASDAQ Capital Market under the symbol "VTGN." No assurance can be given that our application will be approved. There is no established public trading market for the warrants and we do not intend to apply to list the warrants on a securities exchange or automated quotation system.
Risk factors	An investment in our Company is highly speculative and involves a significant degree of risk. See "Risk Factors" beginning on page 6 of this prospectus for a discussion of factors you should carefully consider before investing in our securities.

The number of shares of common stock to be outstanding after this Offering is based on 2,525,276 shares outstanding as of May 6, 2016 and does not include, as of that date:

331,987 shares of common stock issuable upon the exercise of outstanding options under our 1999 Stock Incentive Plan and 2008 Stock Incentive Plan, with a weighted average exercise price of $9.55 per share, of which approximately 196,779 were exercisable as of May 6, 2016;

665,242 shares of common stock reserved for issuance in connection with future grants under our 2008 Stock Incentive Plan;

1,901,103 shares of common stock that have been reserved for issuance upon exercise of outstanding warrants, which have exercise prices ranging from $7.00 per share to $30.00 per share, and a weighted average exercise price of $8.17 per share;

750,000 shares of common stock reserved for issuance upon conversion of 500,000 shares our Series A Preferred Stock (Series A Preferred);

1,173,669 shares of common stock reserved for issuance upon conversion of the same number of shares of our 10% Series B Convertible Preferred Stock (Series B Preferred) which are not subject to automatic conversion into an equal number of shares of common stock upon completion of this Offering;

2,318,012 shares of common stock reserved for issuance upon the exchange of Series C Convertible Preferred Stock (Series C Preferred); and

Up to 2,352,942 shares of common stock issuable upon exercise of warrants to be issued to purchasers in this Offering at an exercise price equal to 125% of the per share offering price.

Unless otherwise indicated, this prospectus reflects and assumes the following:

- no exercise of options or warrants outstanding as of May 6, 2016;
- the automatic conversion of approximately 2,521,622 shares of our Series B Preferred, which conversions will automatically take place upon consummation of the Offering, and the issuance of approximately 220,453 shares of common stock as payment of accrued but unpaid dividends on those shares of Series B Preferred automatically converted upon completion of the Offering; and
- no exercise by the underwriters of their option to purchase up to 352,942 additional shares of common stock and/or warrants to purchase up to 352,942 shares of common stock from us, and no exercise of the warrants issued to the purchasers in connection with this Offering.

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SUMMARY CONSOLIDATED FINANCIAL DATA

The following tables summarize our consolidated financial data. We have derived the summary consolidated statement of operations data for the years ended March 31, 2015 and 2014 from our audited consolidated financial statements included elsewhere in this prospectus. We have derived the summary consolidated statement of operations data for the nine-months ended December 31, 2015 and 2014 and our balance sheet data as of December 31, 2015 from our unaudited interim consolidated financial statements included elsewhere in this prospectus. The unaudited interim consolidated financial statements have been prepared on the same basis as the audited consolidated financial statements and reflect, in our opinion, only adjustments of a normal, recurring nature that are necessary for a fair statement of the unaudited interim consolidated financial statements. Our results for the nine months ended December 31, 2015 are not necessarily indicative of results to be expected for the full year or any other period. The following summary consolidated financial data should be read in conjunction with the section titled “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and our consolidated financial statements and related notes included elsewhere in this prospectus.

	Fiscal Year Ended March 31,		Nine-Months Ended December 31,	
	2015	2014	2015	2014
Consolidated Statement of Operations Data:	(in thousands, except per share amounts)			
Operating expenses:				
Research and development	$ 2,433	$ 2,481	$ 2,835	$ 1,477
General and administrative	4,344	2,548	6,515	2,024
Total operating expenses	6,777	5,029	9,350	3,501
Loss from operations	(6,777)	(5,029)	(9,350)	(3,501)
Other expenses, net:				
Interest expense, net	(4,549)	(1,503)	(770)	(2,183)
Change in warrant liabilities	(35)	3,567	(1,895)	528
Loss on early extinguishment of debt	(2,388)	-	(26,700)	(2,371)
Other expense	(135)	-	(2)	(135)
Loss before income taxes	(13,884)	(2,965)	(38,717)	(7,662)
Income taxes	(2)	(3)	(2)	(2)
Net loss	(13,886)	(2,968)	(38,719)	(7,664)
Accrued dividend on Series B Preferred Stock	-	-	(1,459)	-
Deemed dividend on Series B Preferred Units	-	-	(1,812)	-
Net loss attributable to common stockholders	$ (13,886)	$ (2,968)	$ (41,990)	$ (7,664)
Basic net loss attributable to common stockholders per common share	$ (10.53)	$ (2.70)	$ (25.45)	$ (6.03)
	$ (10.61)	$ (3.81)	$ (25.45)	$ (6.14)

Diluted net loss attributable to common stockholders per common share				
Weighted average shares used in computing:				
Basic net loss attributable to common stockholders per common share	1,318,797	1,098,742	1,650,160	1,270,495
Diluted net loss attributable to common stockholders per common share	1,318,797	1,099,216	1,650,160	1,288,674

	March 31, 2015	December 31, 2015	
		Actual	Pro Forma(1)
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash and cash equivalents	$ 70	$ 1,158	$
Total assets	$ 270	$ 2,012	$
Current portion of notes payable	$ 13,930	$ 74	$
Working capital	$ (17,282)	$ (215)	$
Common stock and preferred stock and additional paid-in capital	$ 67,948	$ 125,611	$
Total stockholders' deficit	$ (20,543)	$ (1,598)	$

(1) The pro forma column gives effect to the sale and issuance by us of 2,352,942 shares of our common stock in this Offering, assuming an offering price of $[___] per share and warrants to purchase up to 2,352,942 shares of common stock in this Offering at an offering price of $0.01 per warrant, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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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, including our financial statements and related notes, before deciding whether to purchase securities in the Offering. If any of the following risks are realized, our business, financial condition and results of operations could be materially and adversely affected.

Risks Related to Product Development, Regulatory Approval and Commercialization

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

We currently have no drug products for sale and may never be able to develop and commercialize marketable drug products. Our business depends heavily on the successful development, regulatory approval and commercialization of AV-101 for depression, including for MDD, and various other diseases and disorders involving the CNS, as well as our ability to produce, develop and commercialize NCEs from our drug rescue programs. AV-101 will require substantial additional Phase 2 and Phase 3 clinical development, testing and regulatory approval before we are permitted to commence its commercialization and is unlikely to achieve regulatory approval until at least 2020, if at all. Each drug rescue NCE will require substantial non-clinical development, all phases of clinical development, and regulatory approval before we are permitted to commence its commercialization. The non-clinical studies and clinical trials of our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market any product candidate. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through non-clinical studies and clinical trials that the product candidate is safe and effective for use in each target indication. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of any of our non-clinical studies or clinical trials. This process can take many years and may also include post-marketing studies and surveillance, which will require the expenditure of substantial resources beyond the proceeds we have raised to date. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our non-clinical studies and clinical trials, we cannot assure you that AV-101, any drug rescue NCE, or any other product candidate will be successfully developed or commercialized.

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

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

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

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

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

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

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

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

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

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

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

The results of preclinical studies and early clinical trials of AV-101 and other product candidates may not be predictive of the results of later-stage clinical trials. AV-101 or other product candidates in later stages of clinical trials may fail to show the desired safety and efficacy results despite having progressed through preclinical studies and initial clinical trials. Many companies in the biopharmaceutical industry have suffered significant setbacks in

advanced clinical trials due to adverse safety profiles or lack of efficacy, notwithstanding promising results in earlier studies. Similarly, our future clinical trial results may not be successful for these or other reasons.

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

For example, the results of planned clinical trials may be adversely affected if we or our collaborator seek to optimize and scale-up production of a product candidate. In such case, we will need to demonstrate comparability between the newly manufactured drug substance and/or drug product relative to the previously manufactured drug substance and/or drug product. Demonstrating comparability may cause us to incur additional costs or delay initiation or completion of our clinical trials, including the need to initiate a dose escalation study and, if unsuccessful, could require us to complete additional preclinical or clinical studies of our product candidates.

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

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

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

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

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

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

- the FDA may deny permission to proceed with our planned clinical trials or any other clinical trials we may initiate, or may place a clinical trial on hold;
- delays in filing or receiving approvals of additional INDs that may be required;
- negative results from our ongoing pre-clinical studies;
- delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical trials, for example delays in the manufacturing of sufficient supply of finished drug product;

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

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

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

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

delays in validating any endpoints utilized in a clinical trial;

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

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

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

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

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

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

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

changes in government regulations or administrative actions;

problems with clinical supply materials; and

lack of adequate funding to continue clinical trials.

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

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

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

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

have staffing difficulties;

fail to comply with contractual obligations;

experience regulatory compliance issues;

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 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.

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

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

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

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

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

Our reliance on contract manufacturers also exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may appropriate our trade secrets or other proprietary information.

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

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

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

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

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

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

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

the efficacy of our product candidates as demonstrated in clinical trials, and, if required by any applicable regulatory authority in connection with the approval for the applicable indications, to provide patients with incremental health benefits, as compared with other available 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 nonclinical studies and clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other regulatory authorities.

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

- regulatory authorities may withdraw or limit their approval of such product candidates;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we may be required to change the way such product candidates are distributed or administered, conduct additional clinical trials or change the labeling of the product candidates;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to remove such product candidates from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and
- our reputation may suffer.

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

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.

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

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

Currently, management is unaware of any FDA-approved adjunctive therapy for treatment-resistant MDD with the same mechanism of action as AV-101. However, new antidepressant products with other mechanisms of action or products approved for other indications, including the anesthetic ketamine, are being or may be used off-label for treatment of MDD, as well as other CNS indications for which AV-101 may have therapeutic potential. Additionally, other non-pharmaceutical treatment options, such psychotherapy and electroconvulsive therapy (ECT) are sometimes used before or instead of standard antidepressants to treat patients with MDD.

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

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

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

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

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to

such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate. The terms of any collaboration or other arrangements that we may establish may not be favorable to us.

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

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

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

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

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

Because we have limited financial and management resources, we focus on a limited number of research programs and product candidates and are currently focused primarily on our AV-101 candidate, with additional limited focus on NCE drug rescue and RM candidates. 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:

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.

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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 AV-101 as an augmentation therapy for MDD, physicians may nevertheless prescribe AV-101 to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

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

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

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

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

Even if we obtain Orphan Drug designation from the FDA for one or more of our product candidates, there are limitations to exclusivity afforded by such designation. In the United States, the company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years. This orphan drug exclusivity prevents the FDA from approving another application, including a full NDA to market the same drug for the same orphan indication, except in very limited circumstances, including when the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. For purposes of small molecule drugs, the FDA defines “same drug” as a drug that contains the same active moiety and is intended for the same use as the drug in question. To obtain orphan drug exclusivity for a drug that shares the same active moiety as an already approved drug, it must be demonstrated to the FDA that the drug is safer or more effective than the approved orphan designated drug, or that it makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition or if another drug with the same active moiety is determined to be safer, more effective, or represents a major contribution to patient care.

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

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

- our customers' ability to obtain reimbursement for our product candidates in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;
- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- the existence of additional potentially relevant third party intellectual property rights;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

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

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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 discover, as well as produce, develop and commercialize proprietary drug rescue NCEs using our stem cell technology, and we cannot provide any assurance that we will successfully develop and commercialize AV-101 or drug rescue NCEs, or that, if produced, AV-101 or any drug rescue NCE will be successfully commercialized.

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

- our drug rescue research methodology may not be successful in identifying potential drug rescue NCEs;
- competitors may develop alternatives that render our drug rescue NCEs obsolete;
- a drug rescue NCE may, on further study, be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a drug rescue NCE may not be capable of being produced in commercial quantities at an acceptable cost, or at all; or
- a drug rescue NCE may not be accepted as safe and effective by regulatory authorities, patients, the medical community or third-party payors.

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

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

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

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

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

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

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

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

Even if we do produce proprietary drug rescue NCEs, we can give no assurance that we will be able to develop and commercialize them as a marketable drug, on our own or in 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.

CardioSafe 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 upon CardioSafe 3D being more accurate, efficient and clinically predictive than long-established surrogate safety models, including animal cells and live animals, and

immortalized, primary and transformed cells, currently used by pharmaceutical companies and others. We cannot give assurance that CardioSafe 3D will be more efficient or accurate at predicting the heart safety of new drug candidates than the testing models currently used. If CardioSafe 3D fails to provide a meaningful difference compared to existing or new models in predicting the behavior of human heart, respectively, their utility for drug rescue will be limited and our drug rescue business will be adversely affected.

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

To generate revenue from our drug rescue activities, we must produce proprietary drug rescue NCEs for which there proves to be demand within the healthcare marketplace, and, if we intend to out-license a particular drug rescue NCE for development and commercialization prior to market approval, then also among pharmaceutical companies and other potential 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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

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

Risks Related to Our Financial Position 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 December 31, 2015, we had an accumulated deficit of approximately $123.2 million. We do not know whether or when we will become profitable. Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to incur increasing levels of operating losses over the next several years and for the foreseeable future. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' deficit and working capital. We expect our research and development expenses to significantly increase in connection with non-clinical studies and clinical trials of our product candidates. In addition, if we obtain marketing approval for our product candidates, we may incur significant sales, marketing and outsourced-manufacturing expenses should we elect not to collaborate with one or more third parties for such services and capabilities. As a public company, we incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenues. To date, we have generated approximately $16.4 million in revenues, exclusively from the receipt of research and development grants. We have not yet commercialized any product or generated any revenues from product sales, and we do not know when, or if, we will generate any revenue from product sales. We do not expect to generate significant revenue unless and until we obtain marketing approval of, and begin to experience sales of, AV-101, or we enter into one or more 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.

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

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

Our consolidated financial statements for the year ended March 31, 2015 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 or all 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 stem cell technology platform. In particular, we have expended substantial resources advancing AV-101 through preclinical development and Phase 1 clinical safety studies, and developing CardioSafe 3D for drug rescue applications, and we will continue to expend substantial resources for the foreseeable future developing and commercializing AV-101, and, potentially, developing drug rescue NCEs and RM therapies. These expenditures will include costs associated with general and administrative costs, facilities costs, research and development, acquiring new technologies, manufacturing product candidates, conducting preclinical experiments and clinical trials and obtaining regulatory approvals, as well as commercializing any products approved for sale.

At December 31, 2015, our existing cash and cash equivalents were not sufficient to fund our current operations for the next 12 months. As described in Note 8, Capital Stock, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus, on August 3, 2015, we entered into an agreement with Platinum Long Term Growth VII, LLC (Platinum) (August 2015 Agreement) pursuant to which we agreed to sell to Platinum an additional $3.0 million of our Series B Preferred and Series B Warrants (collectively, Series B Units). Through December 31, 2015, Platinum purchased an aggregate of $1.65 million of Series B Units under the August 2015 Agreement. Concurrently with its December 2015 purchase of $1.0 million of Series B Units and at our request, Platinum agreed to cancel its right to purchase the remaining $1.35 million of the Series B Units under the August 2015 Agreement. From January 1, 2016 through April 14, 2016, we have sold to accredited investors other than Platinum $628,000 of our Series B Units in self-placed private placement transactions. In February 2015, we entered into the CRADA with the NIH, under which the NIH is fully funding and conducting the initial Phase 2a clinical efficacy and safety of AV-101 in MDD. However, we have no current source of revenue to sustain our present activities, and we do not expect to generate revenue until, and unless, we (i) out-license or sell AV-101, a drug rescue NCE, or another drug candidate unrelated to AV-101 to third-parties, (ii) enter into license arrangements involving our stem cell technology, or (iii) obtain approval from the FDA or other regulatory authorities and successfully commercialize, on our own or through a future collaboration, one or more of our compounds. As the outcome of our AV-101 and NCE drug rescue activities and future anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates, on our own or in collaboration with others. In addition, other unanticipated costs may arise. As a result of these and other factors, we will need to seek additional capital in the near term to meet our future operating requirements, including capital necessary to obtain regulatory approval for, and to commercialize, our product candidates, and may seek additional capital in the event there exists favorable market

conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. We are considering a range of potential sources of funding, including public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches, and we intend to complete additional financing arrangements in 2016. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

Our future capital requirements depend on many factors, including:

- the number and characteristics of the product candidates we pursue, including AV-101 and drug rescue NCEs;
- the scope, progress, results and costs of researching and developing our product candidates, and conducting preclinical and clinical studies;
- the timing of, and the costs involved in, obtaining regulatory approvals for our product candidates;
- the cost of commercialization activities if any of our product candidates are approved for sale, including marketing, sales and distribution costs;
- the cost of manufacturing our product candidates and any products we successfully commercialize;

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- our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;
- market acceptance of our products;
- the effect of competing technological and market developments;
- our ability to obtain government funding for our programs;
- the costs involved in obtaining and enforcing patents to preserve our intellectual property;
- the costs involved in defending against such claims that we infringe third-party patents or violate other intellectual property rights and the outcome of such litigation;
- the timing, receipt and amount of potential future licensee fees, milestone payments, and sales of, or royalties on, our future products, if any; and
- the extent to which we acquire or invest in businesses, products and technologies, although we currently have no commitments or agreements relating to any of these types of transactions.

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

If we are unable to obtain 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.

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

Although we expect net proceeds from this Offering to provide sufficient funding for our operations through the release of topline results of our fully-funded, NIH-sponsored AV-101 Phase 2a clinical study in major depressive disorder (Phase 2a MDD Study), anticipated in the second quarter of 2017, as well as the launch and conduct of a substantial portion of our AV-101 clinical study in MDD (Phase 2b MDD Study), the net proceeds from the Offering will not be sufficient to complete the Phase 2b MDD Study unless we also receive, prior to the end of the second quarter of 2017, proceeds resulting from the exercise of a substantial portion of the warrants in this Offering and the

underwriters exercise their option to purchase additional shares and warrants. Assuming no exercise of the warrants acquired in this Offering and no exercise of the underwriters' option to purchase additional shares and warrants, we believe an additional $10.0 million to $12.0 million will be required prior to the end of the second quarter of 2017 in order to complete the Phase 2b MDD Study. No assurances can be provided that such additional capital will be available to us when necessary, on reasonable terms, or at all. In the event we are unable to raise such additional capital, our operations will be negatively and materially affected

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

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

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

Since inception, we have received substantial funds under grant award programs funded by state and federal governmental agencies, such as the NIH, the NIH's National Institute of Neurological Disease and Stroke and the 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.

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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 (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.

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 eight full-time employees, which may make us more reliant on our individual employees than companies with a greater number of employees. The loss of services of any of these individuals could delay or prevent the successful development of AV-101, drug rescue NCEs, other product candidates, and other applications of our stem cell technology, including our production and assessment of potential drug recuse NCEs or disrupt our administrative functions.

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

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

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 drug rescue and stem cell technology-related regenerative medicine programs, we will need to expand our research and development capabilities and/or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners and other third parties. Future growth will impose significant added responsibilities on members of management. Our future financial performance and our ability to develop and commercialize our product candidates and to compete effectively will

depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our research and development efforts effectively and hire, train and integrate additional management, administrative and technical personnel. The hiring, training and integration of new employees may be more difficult, costly and/or time-consuming for us because we have fewer resources than a larger organization. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing the company.

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

If we develop AV-101, drug rescue NCEs, other product candidates, or regenerative medicine product candidates, either on our own or in collaboration with others, we will face inherent risks of product liability as a result of the required clinical testing of such product candidates, and will face an even greater risk if we or our collaborators commercialize any such product candidates. For example, we may be sued if AV-101, any drug rescue NCE, other product candidate, or regenerative medicine product candidate we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

decreased demand for products that we may develop;

injury to our reputation;

withdrawal of clinical trial participants;

costs to defend the related litigation;

a diversion of management's time and our resources;

substantial monetary awards to trial participants or patients;

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

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 the NASDAQ Capital 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.

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

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

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

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

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

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

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

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

Risks Related to Our Intellectual Property Rights

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

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

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

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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.

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

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

Our ability to enforce our patent rights depends on our ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor’s 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, particularly considering that the compound patent to AV-101 has expired;

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 also 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.

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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.

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 that 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 was 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.

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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 (USPTO) 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.

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 USPTO, 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.

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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.

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—Intellectual Property” herein for a description of our license agreements, which includes a description of the termination provisions of these agreements.

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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.

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 payments, 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.

Some intellectual property which we have licensed may have been discovered through government funded programs and thus may be subject to federal regulations such as “march-in” rights, certain reporting requirements, and a preference for U.S. industry. Compliance with such regulations may limit our exclusive rights, subject us to expenditure of resources with respect to reporting requirements, and limit our ability to contract with non-U.S. manufacturers.

Some of the intellectual property rights we have licensed or license in the future may have been generated through the use of U.S. government funding and may therefore be subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980 (Bayh-Dole Act). These U.S. 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, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines 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 (also referred to as “march-in rights”). The U.S. government also has the right to take title to these inventions if we fail, or the applicable licensor fails, 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 to these inventions in any country in which a patent application is not filed within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us, or the applicable licensor, to expend substantial resources. In addition, the U.S. government requires that any products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the U.S. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the U.S. or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property.

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In the event we apply for additional U.S. government funding, and we discover compounds or drug candidates as a result of such funding, intellectual property rights to such discoveries may be subject to the applicable provisions of the Bayh-Dole Act.

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.

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. Additionally, on March 4, 2014, the USPTO 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. Further, in 2015, in Ariosa

Diagnostics, Inc. v. Sequenom, Inc., the Court of Appeals for the Federal Circuit held that methods for detecting fetal genetic defects were not patent eligible subject matter.

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 USPTO, 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.

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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; and
- 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.

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Risks Related to our Securities

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. 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. Although we have applied for listing on the NASDAQ Capital Market and intend to uplist concurrently upon completion of this Offering, no assurances can be given that we will be successful. Until our common stock is listed on that market or a broader exchange, we anticipate that it will remain quoted on the OTCQB. 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.

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 OTCQB, 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.

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

Sales or issuances of a substantial number of shares of our common stock in the public market, or the perception that these sales or issuances are occurring or 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 frequently 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.

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 highly limited public market for shares of our common stock on the OTCQB. Future sales and issuances of a substantial number of shares of our common stock in the public market, including shares issued upon the conversion of our Series A Preferred, Series B Preferred or Series C Preferred, and the exercise of outstanding options and warrants for common stock which are issuable upon exercise, including warrants offered in the Offering, in the public market, or the perception that these sales and issuances are occurring or 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, including Platinum and its affiliate, own a substantial portion of our outstanding capital stock, including our common stock, all of our Series A Preferred, a substantial portion of our Series B Preferred, and all of our Series C Preferred, all of which preferred stock is convertible into a substantial number of shares of common stock. Accordingly, Platinum and other institutional 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.

Following approval by our stockholders in October 2011, our Articles of Incorporation (the Articles) permit us to issue up to 10.0 million shares of preferred stock. Our Board of Directors has authorized the issuance of (i) 500,000 shares of Series A Preferred, all of which shares are currently issued and outstanding; (ii) 4.0 million shares of Series B 10% Convertible Preferred stock, of which approximately 3.7 million shares are issued and outstanding as of May 6, 2016; and (iii) 3.0 million shares of Series C Convertible Preferred Stock, of which approximately 2.3 million shares are issued and outstanding as of May 6, 2016. 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.

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We do not intend to pay dividends on our common stock and, consequently, our stockholders' ability to achieve a return on their 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 our stockholders purchased them.

We incur significant costs to ensure compliance with corporate governance, federal securities law and accounting requirements.

Since becoming a public company by means of a reverse merger in 2011, we have been subject to the reporting requirements of the Securities Exchange Act of 1934, as amended (Exchange Act), which requires that we file annual, quarterly and current reports with respect to our business and financial condition, and the rules and regulations implemented by the SEC, the Sarbanes-Oxley Act of 2002, the Dodd-Frank Act, and the Public Company Accounting Oversight Board, each of which imposes additional reporting and other obligations on public companies. We have incurred and will continue to incur significant costs to comply with these public company reporting requirements, including accounting and related audit costs, legal costs to comply with corporate governance requirements and other costs of operating as a public company. These legal and financial compliance costs will continue to require us to divert a significant amount of money that we could otherwise use to achieve our research and development and other strategic objectives.

The filing and internal control reporting requirements imposed by federal securities laws, rules and regulations on companies that are not "smaller reporting companies" under federal securities laws are rigorous and, once we are no longer a smaller reporting company, we may not be able to meet them, resulting in a possible decline in the price of our common stock and our inability to obtain future financing. Certain of these requirements may require us to carry out activities we have not done previously and complying with such requirements may divert management's attention from other business concerns, which could have a material adverse effect on our business, results of operations, financial condition and cash flows. Any failure to adequately comply with applicable federal securities laws, rules or regulations could subject us to fines or regulatory actions, which may materially adversely affect our business, results of operations and financial condition.

In addition, changing laws, regulations and standards relating to corporate governance and public disclosure are creating uncertainty for public companies, increasing legal and financial compliance costs and making some activities more time consuming. These laws, regulations and standards are subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices. We will continue to invest resources to comply with evolving laws, regulations and standards, however this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If our efforts to comply with new laws, regulations and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to their application and practice, regulatory authorities may initiate legal proceedings against us and our business may be adversely affected.

Our common stock may be considered a "penny stock", and thereby be subject to additional sale and trading regulations that may make it more difficult to sell.

Our common stock may be considered to be a “penny stock” if it does not qualify for one of the exemptions from the definition of “penny stock” under Section 3a51-1 of the Exchange Act. Our common stock may be a “penny stock” if it meets one or more of the following conditions: (i) the stock trades at a price less than $5 per share; (ii) it is not traded on a “recognized” national exchange; or (iii) is issued by a company that has been in business less than three years with net tangible assets less than $5 million.

The principal result or effect of being designated a “penny stock” is that securities broker-dealers participating in sales of our common stock will be subject to the “penny stock” regulations set forth in Rules 15g-2 through 15g-9 promulgated under the Exchange Act. For example, Rule 15g-2 requires broker-dealers dealing in penny stocks to provide potential investors with a document disclosing the risks of penny stocks and to obtain a manually signed and dated written receipt of the document at least two business days before effecting any transaction in a penny stock for the investor’s account. Moreover, Rule 15g-9 requires broker-dealers in penny stocks to approve the account of any investor for transactions in such stocks before selling any penny stock to that investor. This procedure requires the broker-dealer to: (i) obtain from the investor information concerning his or her financial situation, investment experience and investment objectives; (ii) reasonably determine, based on that information, that transactions in penny stocks are suitable for the investor and that the investor has sufficient knowledge and experience as to be reasonably capable of evaluating the risks of penny stock transactions; (iii) provide the investor with a written statement setting forth the basis on which the broker-dealer made the determination in (ii) above; and (iv) receive a signed and dated copy of such statement from the investor, confirming that it accurately reflects the investor’s financial situation, investment experience and investment objectives. Compliance with these requirements may make it more difficult and time consuming for holders of our common stock to resell their shares to third parties or to otherwise dispose of them in the market or otherwise.

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FINRA sales practice requirements may also limit your ability to buy and sell our common stock, which could depress the price of our shares.

Financial Industry Regulatory Authority, Inc. (FINRA) rules require broker-dealers to have reasonable grounds for believing that an investment is suitable for a customer before recommending that investment to the customer. Prior to recommending speculative low-priced securities to their non-institutional customers, broker-dealers must make reasonable efforts to obtain information about the customer's financial status, tax status and investment objectives, among other things. Under interpretations of these rules, FINRA believes that there is a high probability such speculative low-priced securities will not be suitable for at least some customers. Thus, FINRA requirements make it more difficult for broker-dealers to recommend that their customers buy our common stock, which may limit your ability to buy and sell our shares, have an adverse effect on the market for our shares, and thereby depress our share price.

Risks Related to this Offering

Purchasers in this Offering will experience immediate and substantial dilution in the book value of their investment.

If we successfully sell all securities registered by this Offering and investors exercise all warrants included in this Offering, new investors will own approximately 47.6% of our outstanding common stock. In addition, we have issued options, warrants or other derivative securities to acquire common stock at prices below the public offering price. To the extent outstanding options, warrants or other derivative securities are ultimately exercised or converted, or if we issue restricted stock to our employees under our equity incentive plans, there will be further dilution to investors who purchase shares in this Offering. In addition, if we issue additional equity securities or derivative securities, investors purchasing shares in this Offering will experience additional dilution. For a further description of the dilution that you will experience immediately after this Offering, see "Dilution."

We may allocate the net proceeds from this Offering in ways that differ from our estimates based on our current plans and assumptions discussed in the section titled "Use of Proceeds" and with which you may not agree.

The allocation of net proceeds of the Offering set forth in the "Use of Proceeds" section of this prospectus represents our estimates based upon our current plans and assumptions regarding industry and general economic conditions, our future revenues and expenditures. The amounts and timing of our actual expenditures will depend on numerous factors, including market conditions, cash generated by our operations, business developments and related rate of growth. We may find it necessary or advisable to use portions of the proceeds from this Offering for other purposes. Circumstances that may give rise to a change in the use of proceeds and the alternate purposes for which the proceeds may be used are discussed in the section in this prospectus entitled "Use of Proceeds". You may not have an opportunity to evaluate the economic, financial or other information on which we base our decisions on how to use our proceeds. As a result, you and other stockholders may not agree with our decisions. See "Use of Proceeds" for additional information.

The warrants are speculative in nature.

The warrants offered by us in this Offering do not confer any rights of ownership of shares of common stock on its holders, such as voting rights or the right to receive dividends, but only represent the right to acquire shares of common stock at a fixed price for a limited period of time. Specifically, commencing on the date of issuance, holders of the warrants may exercise their right to acquire the shares of common stock and pay an expected exercise price of $[_____] per share, subject to adjustment upon certain events, prior to five years from the date of issuance, after which date any unexercised warrants will expire and have no further value.

There is no established public trading market for the warrants being offered in this Offering and we do not intend to apply to list the warrants on a securities exchange or automated quotation system.

There is no established public trading market for the warrants being offered in this Offering. We do not intend to apply to list the warrants on a securities exchange or automated quotation system. Without an active trading market, the liquidity of warrants will be limited.

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USE OF PROCEEDS

We estimate that the net proceeds to us from this Offering will be approximately $[____] million, or approximately $[____] million if the underwriters exercise their option to purchase additional shares, and/or warrants, from us in full, assuming an offering price of $[____] per share and $0.01 per warrant, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. Each $1.00 increase (decrease) in the assumed public offering price of $[___] per share would increase (decrease) the net proceeds to us from this Offering by approximately $[___] million, or approximately $[___] million if the underwriters exercise their over-allotment option in full, assuming the number of shares offered by us, as set forth on the cover page of this prospectus, remain the same and after deducting estimated underwriting discounts and commissions and estimated Offering expenses payable by us.

We expect to use the net proceeds from this Offering (including proceeds resulting from the exercise of warrants, if any) on (i) manufacturing and regulatory activities required to support the anticipated launch in the fourth quarter of 2016 of our potentially pivotal Phase 2b MDD Study, (ii) launch and conduct of a substantial portion of the Phase 2b MDD Study, (iii) nonclinical development related to our stem cell technology platform, with emphasis on drug rescue, and (iv) other general corporate purposes, including satisfying accounts payable. The table below reflects our current planned use of the net proceeds from this Offering, assuming no exercise of the warrants and no exercise of the underwriters' option to purchase additional shares and warrants. Each of these amounts is an estimate only, and is subject to change at any time before or after closing of the Offering.

	Amounts in $000
Assumed gross proceeds	$ 10,000
Underwriting discounts, commissions and other expenses of the Offering	$ (1,232)
Net proceeds	$ 8,768
Research and development:	
Operations	$ 1,870
Preparation, launch and partial conduct of AV-101 Phase 2b MDD Study	$ 3,562
Nonclinical development of stem cell technology platform drug	$ 507
Total research and development	$ 5,939
General and administrative, working capital and other general corporate purposes, including payment of accounts payable	$ 2,829
	$ 8,768

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

Pending other uses, we intend to invest our proceeds from the Offering in short-term investments or hold them as cash. We cannot predict whether the proceeds invested will yield a favorable return. Our management will have broad discretion in the use of the net proceeds from the Offering, and investors will be relying on the judgment of our management regarding the application of the net proceeds.

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MARKET FOR OUR COMMON STOCK

Market Information

Currently, our common stock is quoted for trading on the OTCQB under the symbol “VSTA.”

We have applied for listing of our common stock on the NASDAQ Capital Market under the symbol “VTGN.” Although we believe we will satisfy NASDAQ listing requirements, no assurance can be given that such listing will be achieved in a timely manner or at all. There is no established public trading market for the warrants and we do not intend to apply to list the warrants on any securities exchange or automated quotation system.

Shown below is the range of high and low sales prices for our common stock for the periods indicated as reported by the OTCQB. The market quotations reflect inter-dealer prices, without retail mark-up, markdown or commissions and may not necessarily represent actual transactions.

	High	Low
Year Ending March 31, 2017		
First quarter ending June 30, 2016 (through May 6, 2016)	$ 9.00	$ 6.00
Year Ending March 31, 2016		
First quarter ending June 30, 2015	$ 16.50	$ 8.00
Second quarter ending September 30, 2015	$ 14.90	$ 6.50
Third quarter ending December 31, 2015	$ 10.25	$ 4.00
Fourth quarter ending March 31, 2016	$ 9.97	$ 6.50
Year Ending March 31, 2015		
First quarter ending June 30, 2014	$ 14.80	$ 5.60
Second quarter ending September 30, 2014	$ 15.00	$ 7.99
Third quarter ending December 31, 2014	$ 10.50	$ 8.00
Fourth quarter ending March 31, 2014	$ 12.00	$ 3.16
Year Ending March 31, 2014		
First quarter ending June 30, 2013	$ 18.00	$ 12.00
Second quarter ending September 30, 2013	$ 17.80	$ 11.00
Third quarter ending December 31, 2013	$ 12.20	$ 5.20
Fourth quarter ending March 31, 2014	$ 10.00	$ 5.60

On May 6, 2016, the closing price of our common stock on the OTCQB was $7.00 per share. Quotes on the OTCQB may not be indicative of the market price of our common stock on a national securities exchange, including the NASDAQ Capital Market.

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DIVIDEND POLICY

We have never declared or paid cash dividends on our capital stock. We currently intend to retain all available funds for use in the operation and expansion of our business, and do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors, subject to applicable laws, and will depend on a number of factors, including our financial condition, results of operations, capital requirements, contractual restrictions, general business conditions and other factors that our board of directors may deem relevant.

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DILUTION

If you invest in our common stock you will experience dilution immediately to the extent of the difference between the public offering price per share of our common stock you pay in this Offering, and the pro forma net tangible book value per share of our common stock immediately after this Offering. As of December 31, 2015, our historical net tangible book value (deficit) was approximately ($1.6) million, or ($0.87) per share of common stock. This calculation does not reflect any dilution associated with the sale and exercise of the warrants offered hereby. As of December 31, 2015, our pro forma net tangible book value (deficit) was approximately $[ ] million, or $[___] per share of common stock. Pro forma net tangible book value per share (deficit) is determined by dividing our total tangible assets less total liabilities, by the number of outstanding shares of our common stock, assuming we issue the maximum amount of securities registered herein.

Dilution in pro forma net tangible book value (deficit) per share represents the difference between the amount per share paid by buyers of shares of our common stock in this Offering and the pro forma net tangible book value (deficit) per share of our common stock immediately following this Offering. After giving effect to the issuance of 2,352,942 shares of common stock at an assumed offering price of $[___] per share, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value (deficit) as of December 31, 2015, would have been approximately $[___] million, or $[___] per share of common stock. This data represents an immediate increase in pro forma net tangible book value of $[___] per share to existing stockholders and an immediate dilution of $[___] per share to new investors purchasing shares at the offering price.

The following table illustrates the per share dilution to investors in this Offering:

Assumed public offering price per share	$
Historical net tangible book value (deficit) per share as of December 31, 2015	$
Increase in pro forma net tangible book value per share attributable to investors in this Offering	
Pro forma net tangible book value (deficit) per share as of December 31, 2015, as adjusted to give effect to this Offering	$
Less: Pro forma as adjusted dilution per share to investors in this Offering	$

Each $1.00 increase (decrease) in the assumed public offering price of $[____] per share, would increase (decrease) our as adjusted net tangible book value after this Offering by approximately $[____] million, or approximately $[____] per share, and the dilution per share to new investors by approximately $[____] per share, assuming that the number of shares offered by us, as set forth on the cover page of this prospectus, remain the same and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. We may also increase or decrease the number of shares we are offering. An increase of 1,000,000 shares in the number of shares offered by us would increase our as adjusted net tangible book value after this Offering by approximately $[____] million, or $[____] per share, and decrease the dilution per share to new investors by $[____] per share, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. Similarly, a decrease of 1,000,000 shares in the number of shares offered by us would decrease our as adjusted net tangible book value after this Offering by approximately $[____] million, or $[____] per share, and increase the dilution per share to new investors by $[____] per share, assuming that the assumed public offering price remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us. The information discussed above is illustrative only and will adjust based on the actual public offering price and other terms of this Offering determined at pricing.

If the underwriters' option to purchase additional shares is exercised in full, the pro forma as adjusted net tangible book value per share of our common stock, as adjusted to give effect to this Offering, would be $[____] per share, and the dilution in pro forma net tangible book value per share to new investors in this Offering would be $[____] per share.

The outstanding share information set forth above is as of December 31, 2015 and excludes, as of that date:

296,738 shares of common stock issuable upon the exercise of outstanding options under our 1999 Stock Incentive Plan and 2008 Stock Incentive Plan;

700,491 shares of common stock reserved for issuance in connection with future grants under our stock 2008 Stock Incentive Plan;

4,971,497 shares of common stock reserved for issuance upon exercise of outstanding warrants, which have exercise prices ranging from $7.00 per share to $30.00 per share;

750,000 shares of common stock reserved for issuance upon conversion of our Series A Preferred; and

3,588,863 shares of common stock reserved for issuance upon conversion of our Series B Preferred.

The outstanding share information set forth above does not include up to 2,352,942 shares of common stock issuable upon exercise of warrants being offered in this Offering, shares of Series B Preferred issued subsequent to December 31, 2015, or shares of common stock reserved for issuance upon exchange of our Series C Preferred, as the Series C Preferred was created and issued subsequent to December 31, 2015.

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CAPITALIZATION

The following table sets forth our capitalization as of December 31, 2015 that is derived from our unaudited financial information included elsewhere in this prospectus:

- on an actual basis; and
- on a pro forma basis, giving effect to the sale and issuance by us of 2,352,942 shares of common stock in this Offering, at an offering price of $[_____] per share and warrants to purchase up to 2,352,942 shares of common stock in this Offering, at an offering price of $0.01 per warrant, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

As of December 31, 2015 (amounts in dollars, and in thousands)	Actual	Pro forma
Cash and cash equivalents	$ 1,158	$ _____
Long-term debt, excluding current portion	29	_____
Stockholders' equity (deficit):		
Preferred stock, $0.001 par value, 10,000,000 shares authorized:		
Series A Preferred, 500,000 shares authorized and outstanding, actual and pro forma	1	
Series B Preferred, 4,000,000 shares authorized and 3,588,863 shares outstanding, actual; 4,000,000 authorized and 1,173,669 shares outstanding, pro forma	4	
Common stock, $0.001 par value, 30,000,000 shares authorized; 1,965,170 shares issued, actual; 7,576,842 shares issued, pro forma	2	_____
Additional paid-in capital	125,605	_____
Treasury stock, at cost, 135,665 shares, actual; 135,665 shares, pro forma	(3,968)	_____
Accumulated deficit	(123,242)	
Total stockholders' deficit	(1,598)	
Total capitalization	$ (411)	$

Common stock outstanding in the table above excludes the following shares as of December 31, 2015:

296,738 shares of common stock issuable upon the exercise of outstanding options under our 1999 Stock Incentive Plan and 2008 Stock Incentive Plan;

700,491 shares of common stock reserved for issuance in connection with future grants under our stock 2008 Stock Incentive Plan;

4,971,497 shares of common stock reserved for issuance upon exercise of outstanding warrants, which have exercise prices ranging from $7.00 per share to $30.00 per share; and

2,352,942 shares of common stock issuable upon exercise of warrants to be issued to purchasers in this Offering at an exercise price equal to 125% of the per share offering price.

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SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data of VistaGen Therapeutics, Inc. should be read in conjunction with, and are qualified by reference to, the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the consolidated financial statements and notes thereto included elsewhere in this prospectus. The consolidated statement of operations data for the years ended March 31, 2015 and 2014, and the consolidated balance sheet data as of March 31, 2015 and 2014 are derived from, and qualified by reference to, our audited consolidated financial statements included elsewhere in this prospectus and should be read in conjunction with those consolidated financial statements and notes thereto. The consolidated statement of operations data for the nine month periods ended December 31, 2015 and 2014 and the consolidated balance sheet data as of December 31, 2015 are derived from our unaudited consolidated financial statements included elsewhere in this prospectus which, in our opinion, have been prepared on the same basis as the audited consolidated financial statements and reflect only adjustments, consisting only of normal recurring adjustments, necessary for a fair presentation of our results of operations and financial position. Our results for the nine months ended December 31, 2015 are not necessarily indicative of results to be expected for the full year or any other period.

	Fiscal Year Ended March 31,		Nine-Months Ended December 31,	
	2015	2014	2015	2014
Consolidated Statement of Operations Data:	(in thousands, except per share amounts)			
Operating expenses:				
Research and development	$ 2,433	$ 2,481	$ 2,835	$ 1,477
General and administrative	4,344	2,548	6,515	2,024
Total operating expenses	6,777	5,029	9,350	3,501
Loss from operations	(6,777)	(5,029)	(9,350)	(3,501)
Other expenses, net:				
Interest expense, net	(4,549)	(1,503)	(770)	(2,183)
Change in warrant liabilities	(35)	3,567	(1,895)	528
Loss on early extinguishment of debt	(2,388)	-	(26,700)	(2,371)
Other expense	(135)	-	(2)	(135)
Loss before income taxes	(13,884)	(2,965)	(38,717)	(7,662)
Income taxes	(2)	(3)	(2)	(2)
Net loss	(13,886)	(2,968)	(38,719)	(7,664)
Accrued dividend on Series B Preferred Stock	-	-	(1,459)	-
Deemed dividend on Series B Preferred Units	-	-	(1,812)	-
Net loss attributable to common stockholders	$ (13,886)	$ (2,968)	$ (41,990)	$ (7,664)
Basic net loss attributable to common stockholders per common share	$ (10.53)	$ (2.70)	$ (25.45)	$ (6.03)
Diluted net loss attributable to common stockholders per common share	$ (10.61)	$ (3.81)	$ (25.45)	$ (6.14)
Weighted average shares used in computing:				
Basic net loss attributable to common stockholders per common share	1,318,797	1,098,742	1,650,160	1,270,495

Diluted net loss attributable to common stockholders per common share	1,318,797	1,099,216	1,650,160	1,288,674

	As of March 31,		As of December 31,
	2015	2014	2015
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash and cash equivalents	$ 70	$ –	$ 1,158
Total assets	$ 270	$ 264	$ 2,012
Current portion of notes payable	$ 13,930	$ 2,129	$ 74
Working capital	$ (17,282)	$ (5,165)	$ (215)
Common stock and preferred stock additional paid-in capital	$ 67,948	$ 62,003	$ 125,611
Total stockholders' deficit	$ (20,543)	$ (12,780)	$ (1,598)

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MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion of our financial condition and results of operations in conjunction with the financial statements and the notes thereto included elsewhere in this prospectus. The following discussion contains forward-looking statements that reflect our plans, estimates and beliefs. Our actual results could differ materially from those discussed in the forward-looking statements. Factors that could cause or contribute to these differences include those discussed below and elsewhere in this prospectus, particularly in “Risk Factors.”

Overview

We are a clinical-stage biopharmaceutical company dedicated to developing and commercializing innovative product candidates for patients with diseases and disorders involving the CNS. Our lead product candidate, AV-101, is a next generation, orally available prodrug candidate in Phase 2 development, initially for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants.

AV-101’s mechanism of action, as an NMDAR antagonist binding selectively at the GlyB co-agonist site of the NMDAR, is fundamentally differentiated from all standard antidepressants, as well as all atypical antipsychotics used adjunctively with standard antidepressants, currently approved by the FDA.

Our ongoing Phase 2a clinical study of AV-101 in subjects with treatment-resistant MDD is being conducted and funded by the NIMH under our February 2015 CRADA with the NIMH. The first patient in this NIMH-sponsored Phase 2a study was dosed in November 2015. The Principal Investigator of the study is Dr. Carlos Zarate, Jr., Chief of the NIMH’s Experimental Therapeutics & Pathophysiology Branch and its Section on Neurobiology and Treatment of Mood and Anxiety Disorders. Previous NIMH studies, including studies conducted by Dr. Zarate, have focused on the effects of I.V. ketamine on depression. These NIMH studies have demonstrated robust antidepressant effects in patients with treatment-resistant MDD within hours of a single low dose of I.V. ketamine and stimulated research and development around a new generation of antidepressants with potential to deliver ketamine-like fast-onset benefits without its side effects.

Currently, we are preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. We anticipate commencement of this potentially pivotal, multi-center, multi-dose, double blind, placebo-controlled Phase 2b efficacy and safety study in the fourth quarter of 2016. Dr. Maurizio Fava, Professor of Psychiatry at Harvard Medical School and Director, Division of Clinical Research, MGH Research Institute and Executive Director, MGH Clinical Trials Network and Institute, will be the Principal Investigator of our Phase 2b study.

We also believe AV-101 has broad therapeutic utility with multiple near term CNS pipeline expansion opportunities, including chronic neuropathic pain, epilepsy, Huntington’s disease and Parkinson’s disease.

In addition to clinical development of AV-101, we are also focused on establishing strategic collaborations to advance potential commercial applications of our hPSC technology platform, including drug rescue to develop proprietary NCEs for our internal drug candidate pipeline, and RM using blood, cartilage, heart and liver cells derived from our hPSC technology.

The Merger

VistaGen Therapeutics, Inc., a California corporation incorporated on May 26, 1998 (VistaGen California), is our wholly owned subsidiary. Excaliber Enterprises, Ltd. (Excaliber), a publicly held company (formerly OTCBB:

EXCA) was incorporated under the laws of the State of Nevada on October 6, 2005. Pursuant to a strategic merger transaction on May 11, 2011, Excaliber acquired all outstanding shares of VistaGen California in exchange for 341,823 shares of our common stock and assumed all of VistaGen California's pre-Merger obligations (the Merger). Shortly after the Merger, Excaliber's name was changed to "VistaGen Therapeutics, Inc." (a Nevada corporation).

VistaGen California, as the accounting acquirer in the Merger, recorded the Merger as the issuance of common stock for the net monetary assets of Excaliber, accompanied by a recapitalization. The accounting treatment for the Merger was identical to that resulting from a reverse acquisition, except that we recorded no goodwill or other intangible assets. A total of 78,450 shares of our common stock, representing the shares held by stockholders of Excaliber immediately prior to the Merger and effected for a post-Merger two-for-one (2:1) stock split, have been reflected as outstanding for all periods presented in the Consolidated Financial Statements for the years ended March 31, 2015 and 2014 of the Company included elsewhere in this prospectus. Additionally, the Consolidated Balance Sheets reflect the $0.001 par value of Excaliber's common stock.

The Consolidated Financial Statements for the years ended March 31, 2015 and 2014 included elsewhere in this prospectus represent the activity of VistaGen California from May 26, 1998, and the consolidated activity of VistaGen California and Excaliber (now VistaGen Therapeutics, Inc., a Nevada corporation), from May 11, 2011 (the date of the Merger). The Consolidated Financial Statements for the years ended March 31, 2015 and 2014 also include the accounts of VistaGen California's two inactive wholly-owned subsidiaries, Artemis Neuroscience, Inc., a Maryland corporation (Artemis), and VistaStem Canada, Inc., a corporation organized under the laws of Ontario, Canada (VistaStem Canada).

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Financial Operations Overview

Net Loss

We have not yet achieved revenue-generating status from any of our product candidates. Since inception, we have devoted substantially all of our time and efforts developing AV-101 from early preclinical studies to our ongoing Phase 2a clinical study in MDD, as well as stem cell research and bioassay development, small molecule drug development, and creating, protecting and patenting intellectual property, with the corollary initiatives of recruiting personnel and raising working capital. As of December 31, 2015, we had an accumulated deficit of approximately $123.2 million. Our net loss for the nine month period ended December 31, 2015 was $38.7 million, including a non-cash loss of approximately $26.7 million attributable to converting over $17.2 million of our indebtedness into equity securities between May 2015 and August 2015. Our net loss for the nine-month period ended December 31, 2014 was $7.7 million. We expect losses to continue for the foreseeable future, primarily related to our further development of AV-101 for MDD and additional CNS indications.

Summary of Fiscal Year 2015 and Nine-Months Ended December 31, 2015

Although our financial resources have been limited, we have continued to advance development of AV-101 for MDD and other CNS indications and explore NCE drug rescue and regenerative medicine opportunities related to our stem cell technology platform. Pursuant to our February 2015 CRADA with the NIH, the NIH is funding and conducting our Phase 2 clinical study of AV-101 in MDD.

Throughout fiscal 2014 and 2015 and the nine months ended December 31, 2015, through self-placed private placement transactions and other corporate finance initiatives, our executive management has been focused on raising sufficient operating capital to continue to advance development of AV-101, as well as other research and development objectives, while meeting our continuing operational needs. Among our most significant accomplishments during the nine months ended December 31, 2015 have been the following: (i) entering into our CRADA with the NIMH; (ii) launching, under the CRADA, our NIH-funded Phase 2a clinical study of AV-101 in subjects with treatment-resistant MDD, with Dr. Carlos Zarate, Jr., Chief of the Section on the Neurobiology and Treatment of Mood Disorders and Chief of the Experimental Therapeutics and Pathophysiology Branch at the NIMH, as Principal Investigator; (iii) bolstering our Clinical and Scientific Advisory Board with the additions of both Dr. Maurizio Fava, Professor of Psychiatry at Harvard Medical School and Director of the Division of Clinical Research of the Massachusetts General Hospital Research Institute, and Dr. Gerard Sanacora, Associate Professor at Yale School of Medicine and Director of the Yale Depression Research Program; (iv) publishing AV-101 preclinical data in the October 2015 issue of the peer-reviewed, Journal of Pharmacology and Experimental Therapeutics, in an article entitled “The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition;” (v) successfully negotiating, extinguishing and converting (in self-placed private placement transactions) approximately $17.2 million (substantially all) of our outstanding indebtedness into our equity securities; and (vi) completing self-placed private placement transactions with accredited investors thereby providing additional operating capital through the sale of our equity securities.

To meet our working capital needs, in April and May 2015, we completed self-placed private placement transactions involving securities purchase agreements with accredited investors pursuant to which we sold to such accredited investors 2014 Private Placement Units, for aggregate cash proceeds of $280,000, consisting of (i) 10% convertible notes in the aggregate face amount of $280,000 due between April 30, 2015 and May 15, 2015; (ii) an aggregate of 33,000 restricted shares of our common stock; and (iii) warrants exercisable through December 31, 2016 to purchase an aggregate of 24,250 restricted shares of our common stock at an exercise price of $10.00 per share. Between May 2015 and December 31, 2015, we entered into self-placed private placement transactions involving securities purchase agreements with accredited investors, pursuant to which we sold Series B Preferred Units, for aggregate cash proceeds

of approximately $4.3 million, consisting of an aggregate of (i) 628,264 shares of our Series B 10% Convertible Preferred Stock (Series B Preferred); and (ii) five-year warrants to purchase an aggregate of 628,264 shares of our common stock. In connection with the foregoing self-placed private placement transactions, from April 1, 2015 and December 31, 2015, we received aggregate cash proceeds of approximately $4.6 million.

As a matter of course, we seek to minimize cash commitments and expenditures for both internal and external research and development and general and administrative services to the greatest extent possible. The conversion of such a substantial portion of our outstanding indebtedness during the nine months ended December 31, 2015 materially reduced our cash requirements for debt service.

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Revenue

We reported no revenue for the fiscal years ended March 31, 2015 or 2014, or for the nine months ended December 31, 2015. We have successfully completed our Phase 1 clinical development of AV-101, our orally available, next generation prodrug candidate in clinical development for the treatment of MDD, with additional potential as a new therapy for neuropathic pain, epilepsy, Parkinson's disease and Huntington's disease. Additionally, as indicated previously, we have entered into a CRADA with the NIH providing for an NIH-sponsored Phase 2 clinical study of AV-101 in MDD beginning in Fall 2015. We presently have no revenue generating arrangements.

Research and Development Expense

Research and development expense consists of both internal and external expenses incurred in drug development activities, costs associated with the development of AV-101, sponsored stem cell research and costs related to the licensing, application and prosecution of our intellectual property. These expenses primarily consist of the following:

salaries and benefits, including stock-based compensation costs, travel and related expense for personnel associated with internal research and development activities;

fees to contract research organizations and other professional service providers for services related to the conduct and analysis of clinical trials and other drug development activities;

fees to third parties for access to licensed technology and costs associated with securing and maintaining patents related to our internally generated inventions:

laboratory supplies and materials;

leasing and depreciation of laboratory equipment; and

allocated costs of facilities and infrastructure.

General and Administrative Expense

General and administrative expense consists primarily of salaries and benefits expense, including stock-based compensation expense, for personnel in executive, finance and accounting, and other support functions. Other costs include professional fees for legal, investor relations and accounting services and other strategic consulting and public company expenses as well as facility costs not otherwise included in research and development expense.

Other Expenses, Net

In both fiscal 2015 and 2014, we incurred interest expense, including significant amounts of non-cash discount amortization attributable to certain notes, on the outstanding balances of our Senior Secured Convertible Promissory Notes issued to Platinum between October 2012 and July 2013, on subordinated convertible promissory notes issued between March 2013 and March 2015 as components of our Unit Private Placements and on unsecured promissory notes issued to various contract research organizations, technology licensors and other professional service providers since fiscal 2011. In fiscal 2015 and 2014, we recorded non-cash expense and income, respectively, related to changes in the fair values of the warrants issued or issuable to Platinum in connection with the various Senior Secured Convertible Promissory Notes we issued to Platinum between October 2012 and July 2013. In fiscal 2015, we incurred non-cash losses on extinguishment of debt resulting from settlements or modifications of indebtedness to

Platinum, to various holders of promissory notes issued in connection with our 2013 Unit Private Placement and scheduled to mature on July 30, 2014, and to a technology licensor and a professional service provider. Additionally, in fiscal 2015 we incurred non-cash expense related to the settlement of a note receivable we accepted in fiscal 2012.

Critical Accounting Policies and Estimates

We consider certain accounting policies related to revenue recognition, impairment of long-lived assets, research and development, stock-based compensation, warrant liability and income taxes to be critical accounting policies that require the use of significant judgments and estimates relating to matters that are inherently uncertain and may result in materially different results under different assumptions and conditions. The preparation of financial statements in conformity with United States generally accepted accounting principles (GAAP) requires us to make estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes to the Consolidated Financial Statements for the years ended March 31, 2015 and 2014. These estimates include useful lives for property and equipment and related depreciation calculations, and assumptions for valuing options, warrants and other stock-based compensation. Our actual results could differ from these estimates.

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Revenue Recognition

Although we do not currently have any such arrangements, we have historically generated revenue principally from collaborative research and development arrangements, technology access fees and government grants. We recognize revenue under the provisions of the SEC issued Staff Accounting Bulletin 104, Topic 13, Revenue Recognition Revised and Updated (SAB 104) and Accounting Standards Codification (ASC) 605-25, Revenue Arrangements-Multiple Element Arrangements (ASC 605-25). Revenue for arrangements not having multiple deliverables, as outlined in ASC 605-25, is recognized once costs are incurred and collectability is reasonably assured.

Revenue arrangements with multiple components are divided into separate units of accounting if certain criteria are met, including whether the delivered component has stand-alone value to the customer. Consideration received is allocated among the separate units of accounting based on their respective selling prices. The selling price for each unit is based on vendor-specific objective evidence (VSOE) if available, third party evidence if VSOE is not available, or estimated selling price if neither VSOE nor third party evidence is available. The applicable revenue recognition criteria are then applied to each of the units.

We recognize revenue when the four basic criteria of revenue recognition are met: (i) a contractual agreement exists; (ii) the transfer of technology has been completed or services have been rendered; (iii) the fee is fixed or determinable; and (iv) collectability is reasonably assured. For each source of revenue, we comply with the above revenue recognition criteria in the following manner:

Collaborative arrangements typically consist of non-refundable and/or exclusive technology access fees, cost reimbursements for specific research and development spending, and various milestone and future product royalty payments. If the delivered technology does not have stand-alone value, the amount of revenue allocable to the delivered technology is deferred. Non-refundable upfront fees with stand-alone value that are not dependent on future performance under these agreements are recognized as revenue when received, and are deferred if we have continuing performance obligations and have no objective and reliable evidence of the fair value of those obligations. We recognize non-refundable upfront technology access fees under agreements in which we have a continuing performance obligation ratably, on a straight-line basis, over the period in which we are obligated to provide services. Cost reimbursements for research and development spending are recognized when the related costs are incurred and when collectability is reasonably assured. Payments received related to substantive, performance-based “at-risk” milestones are recognized as revenue upon achievement of the milestone event specified in the underlying contracts, which represent the culmination of the earnings process. Amounts received in advance are recorded as deferred revenue until the technology is transferred, costs are incurred, or a milestone is reached.

Technology license agreements typically consist of non-refundable upfront license fees, annual minimum access fees and/or royalty payments. Non-refundable upfront license fees and annual minimum payments received with separable stand-alone values are recognized when the technology is transferred or accessed, provided that the technology transferred or accessed is not dependent on the outcome of the continuing research and development efforts. Otherwise, revenue is recognized over the period of our continuing involvement.

Government grant awards, which support our research efforts on specific projects, generally provide for reimbursement of approved costs as defined in the terms of grant awards. We recognize grant revenue when associated project costs are incurred.

Impairment of Long-Lived Assets

In accordance with ASC 360-10, Property, Plant & Equipment -Overall, we review for impairment whenever events or changes in circumstances indicate that the carrying amount of property and equipment may not be recoverable. Determination of recoverability is based on an estimate of undiscounted future cash flows resulting from the use of the asset and its eventual disposition. In the event that such cash flows are not expected to be sufficient to recover the carrying amount of the assets, we write down the assets to their estimated fair values and recognize the loss in the Consolidated Statements of Operations and Comprehensive Loss.

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Research and Development Expenses

Research and development expenses are composed of both internal and external costs. Internal costs include salaries and employment-related expenses of scientific personnel and direct project costs. External research and development expenses consist primarily of costs associated with clinical and non-clinical development of AV-101, our prodrug candidate entering late-stage clinical development for MDD, sponsored stem cell research and development costs, and costs related to the application and prosecution of patents related to our stem cell technology platform and AV-101. All such costs are charged to expense as incurred.

Stock-Based Compensation

We recognize compensation cost for all stock-based awards to employees based on the grant date fair value of the award. We record non-cash, stock-based compensation expense over the period during which the employee is required to perform services in exchange for the award, which generally represents the scheduled vesting period. We have granted no restricted stock awards nor do we have any awards with market or performance conditions. For equity awards to non-employees, we re-measure the fair value of the awards as they vest and the resulting value is recognized as an expense during the period over which the services are performed.

We use the Black-Scholes option-pricing model to estimate the fair value of stock-based awards as of the grant date. The Black-Scholes model is complex and dependent upon key data input estimates. The primary data inputs with the greatest degree of judgment are the expected term of the stock options and the estimated volatility of our stock price. The Black-Scholes model is highly sensitive to changes in these two inputs. The expected term of the options represents the period of time that options granted are expected to be outstanding. We use the simplified method to estimate the expected term as an input into the Black-Scholes option-pricing model. We determine expected volatility using the historical method, which, because of the limited period during which our stock has been publicly traded, is based on the historical daily trading data of the common stock of a peer group of public companies over the expected term of the option.

Warrant Liability

We have issued to Platinum Long Term Growth VII, LLC, our largest investor (Platinum), warrants to purchase a substantial number of unregistered shares of our common stock and, subject to Platinum’s exercise of its rights to exchange shares of our Series A Preferred Stock that it holds, we are obligated to issue to Platinum an additional warrant to purchase unregistered shares of common stock (collectively, the Platinum Warrants). The Platinum Warrants contain an exercise price adjustment feature that will reduce the exercise price of the warrants in the event we subsequently issue equity instruments at a price lower than the exercise price of the Platinum Warrants. We account for the Platinum Warrants as non-cash liabilities and estimate their fair value at the end of each financial reporting period and record the change in the fair value as non-cash expense or non-cash income. The key component in determining the fair value of the Platinum Warrants and the related liability is the market price of our common stock, which is subject to significant fluctuation and is not under our control. The resulting change in the fair value of the warrant liability on our net income or loss is therefore also subject to significant fluctuation and will continue to be so until all of the Platinum Warrants are issued and exercised, amended or expire. Assuming all other fair value inputs remain generally constant, we will record an increase in the warrant liability and non-cash losses when our stock price increases and a decrease in the warrant liability and non-cash gains when our stock price decreases.

Notwithstanding the foregoing, and as described in Note 16, Subsequent Events, to the Consolidated Financial Statements for the fiscal years ended March 31, 2015 and 2014 included in this prospectus, on May 12, 2015, we entered into an agreement with Platinum pursuant to which Platinum agreed to amend the Platinum Warrants to (A) fix the exercise price thereof at $7.00 per share, (B) eliminate the exercise price reset features and (C) fix the number

of shares of our common stock issuable thereunder. This agreement and the related amendments to the Platinum Warrants resulted in the elimination of the warrant liability with respect to the Platinum Warrants during the quarter ending June 30, 2015.

Income Taxes

We account for income taxes using the asset and liability approach for financial reporting purposes. We recognize deferred tax assets and liabilities for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date. Valuation allowances are established, when necessary, to reduce the deferred tax assets to an amount expected to be realized.

Recent Accounting Pronouncements

See Note 3 to the Consolidated Financial Statements included in in this prospectus for information on recent accounting pronouncements.

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Results of Operations

Comparison of Years Ended March 31, 2015 and 2014

The following table summarizes the results of our operations for the fiscal years ended March 31, 2015 and 2014 (amounts in $000):

	Fiscal Years Ended March 31,	
	2015	2014
Operating expenses:		
Research and development	$ 2,433	$ 2,481
General and administrative	4,344	2,548
Total operating expenses	6,777	5,029
Loss from operations	(6,777)	(5,029)
Other expenses, net:		
Interest expense, net	(4,549)	(1,503)
Change in warrant liabilities	(35)	3,567
Loss on extinguishment of debt	(2,388)	-
Other expense	(135)	-
Loss before income taxes	(13,884)	(2,965)
Income taxes	(2)	(3)
Net loss	$ (13,886)	$ (2,968)

Revenue

We reported no revenue for the fiscal years ended March 31, 2015 or 2014. We have successfully completed our Phase 1 development of AV-101. Additionally, as indicated previously, we have entered into a CRADA with the NIH providing for an NIH-sponsored Phase 2 clinical study of AV-101 in MDD, which study began in October 2015.

Research and Development Expense

Research and development expense decreased by 2% in fiscal 2015 compared to fiscal 2014. The following table compares the primary components of research and development expense between the periods (in $000):

	Fiscal Years Ended March 31,	
	2015	2014
Salaries and benefits	$ 889	$ 902
Stock-based compensation	849	453
UHN research under SRCA	-	160
Consulting services	109	53
Technology licenses and royalties	217	484
Project-related third-party research and supplies:		
AV-101	51	51
All other including CardioSafe and LiverSafe	54	145
	105	196
Rent	220	185

Depreciation	44	44
All other	-	4
Total Research and Development Expense	$ 2,433	$ 2,481

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To conserve cash resources, during fiscal 2015 and 2014, Ralph Snodgrass, PhD, our Chief Scientific Officer (CSO), accepted a voluntary cash pay reduction to substantially less than his contractual pay rate. For fiscal 2015, the CSO's actual cash pay represented approximately 52% of his contractual pay rate. In fiscal 2014, the CSO voluntarily agreed to accept a cash pay rate of approximately 82% of his contractual rate, not all of which amount was paid. In fiscal 2015, we have accrued the difference between the CSO's contractual pay rate and his actual cash pay, $147,700, for future payment. In fiscal 2014, we accrued the difference between the CSO's reduced pay rate and his actual cash pay, $100,400, for future payment. Aside from a minimal partial repayment received by the CSO during August 2015, a majority of such accrued amounts for both fiscal 2014 and fiscal 2015 remains unpaid. Pay rates for other scientific personnel remained constant between years. One member of our scientific staff voluntarily resigned at the end of September 2014 and another member has voluntarily reduced her work hours and pay since September 2014.

In January 2015, we granted five-year fully exercisable warrants to purchase an aggregate of 115,000 restricted shares of our common stock at an exercise price of $8.00 per share to our CSO and other scientific consultants and service providers, recognizing approximately $528,000 in stock-based compensation expense. Stock based compensation expense for fiscal 2015 and fiscal 2014 also reflects approximately $176,000 and $297,000, respectively, related to the ratable four-year amortization of option grants made to scientific staff and consultants in October 2013 and March 2014 and earlier. The ratable amortization of stock compensation expense related to certain options granted in October 2012 with a two-year vesting period ceased when the options became fully vested in October 2014. An additional component of stock compensation expense is the amortization attributable to grants of warrants made to our CSO in March 2014 and March 2013, amounting to $145,000 in fiscal 2015 and $156,000 in fiscal 2014. The warrants are being amortized over a two-year vesting period, but are subject to certain vesting acceleration events. No further expense will be recognized with respect to the warrants granted in March 2013.

Our most recent sponsored research project budget under the collaboration agreement with Dr. Gordon Keller's laboratory at UHN ended on September 30, 2013, and we have incurred no sponsored research expense under the agreement since that date. We are engaged in discussions with Dr. Keller and UHN regarding the scope of subsequent sponsored research projects and budget under the agreement, but have not yet finalized such project definitions and budgets.

Consulting services reflects fees paid or accrued for scientific services rendered to us by third parties, primarily by members of our scientific advisory board.

Stem cell technology license expense reflects both recurring annual fees as well as costs for patent prosecution and protection that we are required to fund under the terms of certain of our license agreements. We recognize the latter costs as they are invoiced to us by the licensors and they do not occur ratably throughout the year or between years. Certain of our technology licensors invoiced us for significant legal fees for patent protection and prosecution during fiscal 2014.

AV-101 expenses in both fiscal years 2015 and 2014 primarily reflect the costs associated with monitoring for and responding to potential feedback related to the Phase 1 clinical trial and preparing other reports required under the terms of our prior NIH grant, primarily through our contract research collaborator, Cato Research Ltd.

The increase in rent expense versus FY 2014 reflects the full-year impact of rental costs related to our relocation to our current facilities in late-July 2013.

General and Administrative Expense

General and administrative expense increased by 70% in fiscal 2015 compared to fiscal 2014. The following table compares the primary components of general and administrative expense between the periods (in $000):

	Fiscal Years Ended March 31,	
	2015	2014
Salaries and benefits	$ 714	$ 675
Stock-based compensation	1,611	684
Consulting Services	112	94
Legal, accounting and other professional fees	1,197	340
Investor relations	132	120
Insurance	136	130
Travel and entertainment	71	18
Rent and utilities	155	139
Warrant modification expense	98	205
All other expenses	118	143
Total General and Administrative Expense	$ 4,344	$ 2,548

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To conserve cash resources, during fiscal 2015 and 2014, both Shawn Singh, our Chief Executive Officer (CEO), and Jerrold Dotson, our Chief Financial Officer (CFO), accepted voluntary cash pay reductions to substantially less than their contractual pay rates. For fiscal 2015, the CEO's and CFO's actual cash pay represented approximately 24% and 62%, respectively, of contractual rates. In fiscal 2014, the CEO and CFO voluntarily agreed to accept cash pay rates of approximately 72% and 80%, respectively, of their contractual rates, not all of which amounts were paid. In fiscal 2015, we accrued the difference between the CEO's and CFO's contractual pay rate and his actual cash pay, $264,700 and $96,100, respectively, for future payment. In fiscal 2014, we accrued the difference between the CEO's and CFO's reduced pay rates and his actual cash pay, $125,000 and $56,700, respectively, for future payment. Aside from a minimal partial repayment received by each executive during August 2015, a majority of such accrued amounts for both fiscal 2014 and fiscal 2015 remain unpaid and owing. Offsetting the impact of the accrual to contractual pay rates for the CEO and CFO for fiscal 2015 is the annual impact of the voluntary resignations of two administrative employees in August and November 2013 who have not been replaced. Pay rates for other administrative employees remained stable between the periods presented.

In January 2015, we granted five-year fully exercisable warrants to purchase an aggregate of 271,715 restricted shares of our common stock at an exercise price of $8.00 per share to our CEO and CFO, independent members of our Board of Directors and other consultants and service providers, recognizing approximately $1,229,000 in stock-based compensation expense. Stock based compensation expense for fiscal 2015 and fiscal 2014 also reflects approximately $99,000 and $385,000, respectively, related to the ratable four-year amortization of option grants made to employees and consultants in October 2013 and March 2014 and earlier. The ratable amortization of stock compensation expense related to certain options granted in October 2012 with a two-year vesting period ceased when the options became fully vested in October 2014. An additional component of stock compensation expense is the amortization attributable to grants of warrants made to our CEO, CFO and independent members of our Board of Directors in March 2014 and March 2013, amounting to $283,000 in fiscal 2015 and $299,000 in fiscal 2014. The warrants are being amortized over a two-year vesting period, but are subject to certain vesting acceleration events. No further expense will be recognized with respect to the warrants granted in March 2013.

Consulting services primarily reflects fees paid or accrued for the services of the independent members of our Board of Directors.

The increase in legal, accounting and other professional fees results primarily from the impact of (i) two consulting agreements for strategic advisory and business development services pursuant to which we issued an aggregate of 55,000 restricted shares of our common stock valued at $469,000 at the date of issuance and paid $100,000 as cash compensation for such professional services during fiscal 2015; (ii) direct legal fees aggregating $150,000 related to services provided with respect to our prospective public offering of our equity securities and a proposed private offering of our equity securities; (iii) the expensing of approximately $102,000 of investment banker, banker's counsel, accounting and other fees and costs related to the cancellation of our prospective public offering; (iv) legal and other costs related to the 1:20 reverse split of our common stock in August 2014 and legal and filing fees for our private placement Unit financing offerings; and (v) costs related to temporary employee fees for part-time administrative services.

Outsourced investor relations service expenses are essentially flat between periods; we have conducted no special awareness or other initiatives during either fiscal 2015 or 2014. Travel expenses related to meetings with potential investors in our attempted registered public offering account for the increase compared to fiscal 2014.

The fiscal 2015 increase in rent and utilities expense reflects the full-year impact of increased costs related to our relocation to expanded facilities in late-July 2013.

Warrant modification expense in fiscal 2015 reflects the extension by one year of the term of outstanding warrants otherwise scheduled to expire during calendar 2015, as approved by our Board of Directors in January 2015. Warrant modification expense in fiscal 2014 reflects the impact of October 2013 and December 2013 reductions in the exercise price of certain outstanding warrants, generally from $35.00 per share or $30.00 per share, to $10.00 per share, and in limited cases, the extension of the term of certain outstanding warrants, and from which we used the proceeds of the warrant exercises as a source of short-term working capital.

The fiscal 2015 decrease in other expenses is attributable to one-time relocation costs incurred in fiscal 2014 in connection with our relocation to expanded facilities in late-July 2013.

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Other Expenses, Net

In both fiscal 2015 and 2014, other expenses, net includes interest expense, including non-cash discount amortization, on our outstanding promissory notes, as well as the non-cash impact of changes in the fair value of the warrant liabilities related to warrants issued or issuable to Platinum between October 2012 and July 2013. In fiscal 2015, other expenses, net also includes the non-cash loss on extinguishment of debt resulting from the modification of indebtedness to Platinum, holders of convertible promissory notes originally scheduled to mature on July 30, 2014, and to a technology licensor and a professional service provider. Additionally, in fiscal 2015 we incurred non-cash expense related to the settlement of a note receivable we accepted in fiscal 2012.

The following table compares the primary components of net interest expense between the periods (in $000):

	Fiscal Years Ended March 31,	
	2015	2014
Interest expense on promissory notes	$ 1,238	$ 907
Amortization of discount on promissory notes	3,372	640
Other interest expense, including on capital leases and premium financing	7	15
	4,617	1,562
Effect of foreign currency fluctuations on notes payable	(63)	(49)
Interest income	(5)	(10)
Interest expense, net	$ 4,549	$ 1,503

The increase in interest expense between the periods is primarily attributable to the accrued interest recorded for the issuances between August 2013 and March 2015 of an aggregate of approximately $4.1 million of unsecured 10% convertible promissory notes pursuant to the 2013 Unit Private Placement and the 2014 Unit Private Placement. As a result of the significant inception-date discounts recorded in connection with the Unit Notes, approximately $2.7 million in fiscal 2015; the relatively short period between issuance and maturity over which the discount on the Unit Notes must be amortized, generally less than 12 months; and the accelerating amount of discount amortization recorded using the effective interest rate method as the notes approach maturity, discount amortization expense increased by approximately $2.7 million between the periods shown in the preceding table.

Under the terms of the October 2012 Note Exchange and Purchase Agreement we entered with Platinum, we issued Senior Secured Convertible Promissory Notes and a related Exchange Warrant and Investment Warrants between October 2012 and March 2013. We issued a similar senior secured promissory note and related warrant to Platinum in July 2013. Upon Platinum’s exchange of the shares of our Series A preferred stock it holds into shares of our common stock, we will also be required to issue a Series A Exchange Warrant to Platinum. We determined that certain exercise price and share adjustment features contained in the various warrants require us to treat the warrants as liabilities. Accordingly, we recorded a non-cash warrant liability at its estimated fair value as of the date the warrant was issued or the contract executed. During fiscal 2015, we recognized a non-cash loss of $34,600 related to the net increase in the estimated fair value of these non-cash liabilities since March 31, 2014, which resulted primarily from the change in the market price of our common stock in relation to the exercise price of the warrants and an additional year elapsed in the remaining term for all but the Series A Exchange Warrant. During fiscal 2014, we recognized a non-cash gain of $3,556,900 related to the net decrease in the estimated fair value of the warrant liabilities since March 31, 2013, which resulted primarily from the decrease in the market price of our common stock in relation to the exercise price of the warrants.

As described more fully in Note 8, Convertible Promissory Notes and Other Notes Payable, and Note 9, Capital Stock, in the Consolidated Financial Statements for the Years Ended March 31, 2015 and 2014 included in this prospectus, effective May 31, 2014, we entered into agreements with substantially all holders of our 2013 Unit Notes and 2013 Unit Warrants to amend certain terms of the notes and the warrants. We treated the amendments as an extinguishment of debt for accounting purposes. Accordingly, since the fair value of the amended notes and warrants exceeded the carrying amount of the original notes, we recognized non-cash losses on the extinguishment of debt in the aggregate amount of $526,200 attributable to the amendments. We recognized an additional $241,800 as a non-cash loss on extinguishment of debt as a result of the promissory note, shares of our common stock and warrants issued to Icahn School of Medicine at Mount Sinai in settlement of stem cell technology license maintenance fees and reimbursable patent prosecution costs, as described more completely in Note 9, Capital Stock, to the Consolidated Financial Statements for the fiscal years Ended March 31, 2015 and 2014 included in this prospectus. We recognized a further $16,700 non-cash loss on extinguishment of debt as a result of the shares of our unregistered common stock issued to a professional services provider in settlement of fees for prior services rendered, as also described more completely in Note 9, Capital Stock, to the Consolidated Financial Statements for the fiscal years Ended March 31, 2015 and 2014 included in this prospectus.

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As described more completely in Note 8, Convertible Promissory Notes and Other Notes Payable, to the Consolidated Financial Statements for the fiscal years Ended March 31, 2015 and 2014 included in this prospectus, in July 2014, we entered into an agreement with Platinum, as further amended in September 2014, pursuant to which Platinum agreed to convert into our unregistered equity securities all Senior Notes and accrued but unpaid interest thereon held by Platinum upon our consummation prior to October 31, 2014 (the Closing Date) of either (i) a Private Financing or a Public Offering, each as defined in the agreement. Upon consummation of a Private Financing, the Senior Notes would have converted into that number of unregistered shares of our common stock equal to the Outstanding Balance on the Closing Date, divided by $10.00 per share. Upon consummation of a Public Offering, the Senior Notes would have converted into shares of a newly created Series B Convertible Preferred Stock with an aggregate liquidation preference equal to the Outstanding Balance on the Closing Date. Prior to the agreement, the Senior Notes were convertible, at Platinum's option, at any time prior to maturity at a conversion price of $10.00 per share. The modification of the conversion feature in the Senior Notes was treated as an extinguishment of the debt for accounting purposes. Accordingly, since the fair value of the amended Senior Notes substantially exceeded the carrying amount of the original notes, we recognized a non-cash loss on the extinguishment of debt in the aggregate amount of $1,603,400 attributable to the amendment.

As described in Note 9, Capital Stock, to the Consolidated Financial Statements for the fiscal years Ended March 31, 2015 and 2014 included elsewhere in this Prospectus, in October 2014, we accepted a cash payment of $60,000 as settlement in full for a promissory note issued to us in May 2011 for the purchase of shares of our common stock. At the time of the payment, the principal and accrued interest due to us under the note receivable was $194,900, resulting in a recognized loss of $134,900 related to the settlement.

Comparison of Nine Months Ended December 31, 2015 and 2014

The following table summarizes the results of our operations for the nine months ended December 31, 2015 and 2014 (amounts in thousands).

	Nine Months Ended December 31,	
	2015	2014
Operating expenses:		
Research and development	$ 2,835	$ 1,477
General and administrative	6,515	2,024
Total operating expenses	9,350	3,501
Loss from operations	(9,350)	(3,501)
Interest expense (net)	(770)	(2,183)
Change in warrant liabilities	(1,895)	528
Loss on extinguishment of debt	(26,700)	(2,371)
Other expense	(2)	(135)
Loss before income taxes	(38,717)	(7,662)
Income taxes	(2)	(2)
Net loss	$ (38,719)	$ (7,664)
Accrued dividend on Series B Preferred Stock	(1,459)	-
Deemed dividend on Series B Preferred Stock	(1,812)	-

Net loss attributable to common stockholders	$ (41,990)	$ (7,664)

Revenue

We reported no revenue for the nine-month periods ended December 31, 2015 or 2014 and we presently have no revenue generating arrangements. However, as indicated previously, we have entered into a CRADA with the NIH providing for a Phase 2a clinical study of AV-101 in treatment-resistant MDD. This Phase 2a study, which began in late-2015, is being funded by the NIH and being conducted at the NIMH.

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Research and Development Expense

Research and development expense totaled $2.8 million for the nine months ended December 31, 2015 compared to $1.5 million for the nine months ended December 31, 2014, primarily as a result of noncash expense related to stock based compensation awards granted in September 2015 and warrant modifications made in November 2015, as well as patent- and technology license-related expenses in support of AV-101 and our stem cell technology platforms. The following table indicates the primary components of research and development expense for each of the periods (amounts in thousands):

	Nine Months Ended December 31,	
	2015	2014
Salaries and benefits	$ 628	$ 680
Stock-based compensation	979	265
Consulting and other professional services	51	85
Technology licenses and royalties	646	177
Project-related research and supplies:		
AV-101	161	23
Stem cell and all other	42	49
	203	72
Rent	163	165
Depreciation	29	33
Warrant modification expense	135	-
All other	1	-
Total Research and Development Expense	$ 2,835	$ 1,477

The decrease in salaries and benefits is primarily the result of the voluntary resignation of one member of our scientific staff at the end of September 2014 and the voluntary reduction of work hours and pay by another member of our scientific staff during the period October 2014 through September 2015.

The increase in stock based compensation expense for 2015 reflects the $852,200 fair value, determined using the Black-Scholes Option Pricing Model and the assumptions indicated in Note 2, Summary of Significant Accounting Policies, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus of the September 2015 grant of immediately vested and expensed warrants to purchase 150,000 shares of our common stock granted to our CSO. Stock based compensation expense additionally reflects the ratable amortization of option grants made to scientific staff and consultants, most recently in September 2015, March 2014 and October 2013, as well as the ratable amortization of a warrant grant made to our CSO in March 2014. Our stock options are generally amortized over a two-year or four-year vesting period, and warrants granted to the CSO in March 2014 are being amortized over a three-year vesting period. Essentially all of the option grants made prior to October 2013 and a warrant grant made to our CSO in March 2013 became fully-vested and fully-expensed prior to the quarter ended December 31, 2015.

Consulting services reflects fees paid or accrued for scientific services rendered to us by third parties, primarily by members of our scientific and clinical advisory board.

Technology license expense reflects both recurring annual fees as well as costs for patent prosecution and protection that we are required to fund under the terms of certain of our stem cell technology license agreements, as well as those we elected to make for commercial purposes. We recognize these costs as they are invoiced to us by the licensors and they do not occur ratably throughout the year or between years. Additionally, in 2015, this expense includes significant costs we have incurred to advance, in the U.S. and numerous foreign counties, a number of pending patent applications with respect to AV-101 and our stem cell technology platform.

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AV-101 expenses in both periods presented reflect the costs associated with monitoring for and responding to potential feedback related to the Phase 1 clinical trial and preparing other reports required under the terms of our prior NIH grant, primarily through our contract research collaborator, Cato Research Ltd. An additional level of expense has been incurred during the nine months ended December 31, 2015 to explore and develop more efficient and cost-effective production methods for AV-101 as well as for updating documentation to facilitate the Phase 2 clinical trial of AV-101 in treatment resistant MDD that is being funded and conducted by the NIH. Stem cell and other project related expenses in both periods were nominal.

Warrant modification expense reflects an increase in the fair value attributable to the November 2015 modification of outstanding warrants to purchase an aggregate of 315,000 shares of our common stock previously granted to our CSO and a key scientific advisor to reduce the exercise prices thereof from a range of $9.25 to $12.80 per share to $7.00 per share.

General and Administrative Expense

General and administrative expense was $6.5 million for the nine months ended December 31, 2015 compared to $2.0 million reported for the nine months ended December 31, 2014, primarily as a result of noncash expense of approximately $2.9 million related to stock based compensation awards granted in September 2015 and warrant modifications made in November 2015, as well as increased professional services fees. The following table indicates the primary components of general and administrative expenses for each of the periods (amounts in thousands):

	Nine Months Ended December 31,	
	2015	2014
Salaries and benefits	$ 520	$ 530
Stock-based compensation	2,889	299
Consulting Services	72	84
Legal, accounting and other professional fees	2,113	658
Investor relations	60	98
Insurance	105	103
Travel expenses	73	49
Rent and utilities	116	117
Warrant modification expense	480	-
All other expenses	87	86
Total General and Administrative Expense	$ 6,515	$ 2,024

Administrative employee headcount and pay rates have remained essentially consistent between the periods reported.

The increase in stock based compensation expense for 2015 reflects the $2,840,700 fair value, determined using the Black-Scholes Option Pricing Model and the assumptions indicated in Note 2, Summary of Significant Accounting Policies, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus of the September 2015 grant of immediately vested and expensed warrants to purchase an aggregate of 500,000 shares of our common stock granted to our officers, independent members of our Board of Directors and certain administrative consultants. Stock based compensation expense additionally reflects the ratable amortization of option grants made to administrative staff and consultants, most recently in September 2015, March 2014 and October 2013, as well as the ratable amortization of a warrant grant made to certain officers and independent members of our Board of Directors in March 2014. Our stock options are generally amortized over a

two-year or four-year vesting period, and warrants granted to officers and directors in March 2014 are being amortized over a three-year vesting period. Essentially all of the option grants made prior to October 2013 and warrant grants made to our officers and independent members of our Board of Directors in March 2013 became fully-vested and fully-expensed prior to the quarter ended December 31, 2015.

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Consulting services primarily include fees accrued for the services of independent members of our Board of Directors.

The increase in legal, accounting and other professional service fees results primarily from (i) the $675,000 noncash expense recognized pursuant to the June 30, 2015 grant of an aggregate of 90,000 shares of our Series B Preferred having an aggregate value of $1,350,000 as compensation for financial advisory and corporate development service contracts with two independent contractors for services to be performed through June 30, 2016; (ii) the grant of an aggregate of 50,000 shares of our common stock having an aggregate fair value of $500,000 pursuant to two corporate development contracts initiated during the quarter ended June 30, 2015; (iii) the grant of 25,000 shares of our Series B Preferred having a fair value of $250,000 to legal counsel as compensation for services in connection with our debt restructuring and other corporate finance matters, and (iv) $138,000 of noncash expense attributable to the fair value of 15,750 shares of our unregistered common stock and a five-year warrant to purchase 7,500 unregistered shares of our common stock granted in connection with investment banking services. As described in Note 8, Capital Stock, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2016 included elsewhere in this prospectus, the $1,350,000 fair value of the 90,000 shares of Series B Preferred was recorded as a prepaid expense at the date of the grant and is being expensed ratably over the twelve months ending June 30, 2016. Legal expense for 2015 also includes one-time cash fees associated with the conversion of our promissory notes and other debt into our Series B Preferred. Professional services expense in 2015 reflects a $100,000 reduction in expense related to a contract for strategic advisory and business development services compared to 2014. In both years, accounting service fees include expense related to the annual audit of the prior year financial statements and current quarterly financial statement review services.

The decrease in outsourced investor relations service reflects a reduction in investor relations initiatives during the latter portion of calendar 2015.

In both periods, travel expense reflects costs associated with meetings with accredited investors in connection with the self-placed private placements of our securities, and in 2015, with various creditors in connection with extinguishment of a substantial portion of our indebtedness.

Noncash warrant modification expense in 2015 includes (i) a $122,000 increase in the fair value attributable to the June 2015 strategic modification of outstanding warrants to purchase an aggregate of 54,576 shares of our common stock to reduce the exercise prices thereof, generally from $30.00 per share to $10.00 per share; and (ii) a $358,000 increase in the fair value attributable to the November 2015 modification of outstanding warrants to purchase an aggregate of 808,553 shares of our common stock previously granted to our CEO, CFO, and independent members of our Board of Directors to reduce the exercise prices thereof from a range of $9.25 to $12.80 per share to $7.00 per share.

Interest and Other Expenses, Net

Interest expense, net totaled $769,800 for the nine months ended December 31, 2015 compared to the $2,182,900 reported for the nine months ended December 31, 2014, reflecting the extinguishment of substantially all of our promissory notes and related discounts upon conversion into our Series B Preferred between May 2015 and August 2015. The following table summarizes the primary components of interest expense for each of the periods (amounts in thousands):

	Nine Months Ended December 31,	
	2015	2014
Interest expense on promissory notes	$ 208	$ 909

Amortization of discount on promissory notes	565	1,295
Other interest expense, including on capital leases and premium financing	3	6
	776	2,210
Effect of foreign currency fluctuations on notes payable	(6)	(22)
Interest income	-	(5)
Interest expense, net	$ 770	$ 2,183

The substantial overall decrease in interest expense on promissory notes and the related amortization of discounts on such notes between the periods primarily reflects (i) accrued interest and discount amortization recorded for the issuances between July 2014 and May 2015 of an aggregate of approximately $1.8 million of 10% convertible promissory notes (2014 Unit Notes); and (ii) the offsetting cessation of interest accrual and discount amortization upon the conversion of all outstanding Senior Secured Convertible Notes, 2014 Unit Notes and other outstanding promissory notes aggregating approximately $13.3 million into shares of our Series B Preferred between May 2015 and August 2015.

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Under the terms of our October 2012 Note Exchange and Purchase Agreement with Platinum, we issued certain Senior Secured Convertible Promissory Notes and a related Exchange Warrant and Investment Warrants between October 2012 and July 2013. Upon Platinum's exchange of the shares of our Series A Preferred Stock held by Platinum into shares of our common stock, we will also be required to issue a Series A Exchange Warrant to Platinum. We determined that the various warrants included certain exercise price adjustment features requiring us to treat the warrants as liabilities. Accordingly, we recorded a noncash warrant liability at its estimated fair value as of the date of warrant issuance or contract execution. As described in Note 8, Capital Stock, and Note 4, Fair Value Measurements, to the Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus on May 12, 2015, we entered into an agreement with Platinum pursuant to which we amended the various warrants to fix the exercise price thereof and eliminate the anti-dilution reset features that had previously required the warrants to be treated as liabilities and carried at fair value. Accordingly, during the quarter ended June 30, 2015, we adjusted these warrants to their fair value, estimated to be $4,903,200, reflecting an increase of $1,894,700 since March 31, 2015, resulting primarily from the increase in the market price of our common stock in relation to the exercise price of the warrants, and then subsequently eliminated the entire warrant liability with respect to these warrants. (Refer to Note 10, Subsequent Events, to the Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus regarding the subsequent exchange of these warrants for shares of our Series C Preferred stock.) During the nine months ended December 31, 2014, we recognized noncash gains of $528,300 related to the net decrease in the estimated fair value of the warrant liabilities since March 31, 2014, which resulted primarily from the decrease in the market price of our common stock in relation to the exercise price of the warrants.

As described more completely in Note 7, Convertible Promissory Notes and other Notes Payable, and Note 8, Capital Stock, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus, between May 12, 2015 and December 31, 2015, we have extinguished the outstanding balances of approximately $17.2 million of promissory notes, including our Senior Secured Notes, our 2014 Unit Notes and other debt and certain adjustments thereto that were either already due and payable or would have otherwise matured prior to March 31, 2016 by converting such balances into shares of our Series B Preferred. We treated the conversion of the indebtedness into Series B Preferred as extinguishments of debt for accounting purposes. Since the fair value of the Series B Preferred we negotiated in settlement of the promissory notes and other indebtedness exceeded the carrying value of the debts, we incurred noncash losses on each of the extinguishments. Additionally, under the terms of the Platinum Agreement, we issued to Platinum 400,000 shares of Series B Preferred having an aggregate fair value of $4.0 million and Series B Warrants to purchase 1.2 million shares of our common stock having an aggregate of fair value of $8,270,900. We recognized this aggregate fair value as an additional noncash component of loss on extinguishment of debt. Many of the 2014 Unit Notes that were converted into Series B Preferred contained a beneficial conversion feature at the time they were originally issued. We have accounted for the repurchase of the beneficial conversion feature at the time the 2014 Unit Notes were extinguished and converted, an aggregate of $2,237,100, as a reduction to the loss on extinguishment of debt. We recorded an aggregate net noncash loss of $26.7 million attributable to the extinguishment of the indebtedness converted into Series B Preferred.

During the quarter ended June 30, 2014, we entered into agreements with substantially all holders of our 2013 Unit Notes and 2013 Unit Warrants to amend certain terms of the notes and the warrants to essentially conform them to the 2014 Unit Notes and 2014 Unit Warrants. We treated the amendments as an extinguishment of debt for accounting purposes and recognized noncash losses on the extinguishment of debt in the aggregate amount of $526,200 attributable to the amendments. We also recognized an additional $241,800 as a noncash loss on extinguishment of debt as a result of the promissory note, shares of our common stock and warrants issued to Icahn School of Medicine at Mount Sinai in settlement of stem cell technology license maintenance fees and reimbursable patent prosecution costs during the quarter ended June 30, 2014. In July 2014, we entered into an agreement with Platinum, as further amended in September 2014, pursuant to which Platinum agreed to convert into our unregistered equity securities all then outstanding Senior Secured Notes and related accrued interest held by Platinum upon our consummation prior to

October 31, 2014 of either (i) a Private Financing or a Public Offering, each as defined in the agreement. Prior to the agreement, the Senior Secured Notes were convertible, at Platinum's option, at any time prior to maturity at a conversion price of $10.00 per share. The modification of the conversion feature in the Senior Secured Notes was treated as an extinguishment of the debt for accounting purposes and we recognized a non-cash loss on the extinguishment of debt in the aggregate amount of $1,603,400 attributable to the amendment in the quarter ended September 30, 2014.

In October 2014, we accepted a cash payment of $60,000 as settlement in full for a promissory note issued to us in May 2011 for the purchase of shares of our common stock. At the time of the payment, the principal and accrued interest due to us on the note receivable was $194,900, resulting in a noncash loss of $134,900 related to the settlement recognized in Other Expense in the nine months ended December 31, 2014. Other expense in the nine months ended December 31, 2015 reflects the noncash loss on the disposition of a piece of failed lab equipment.

We allocated the proceeds from the self-placed private placement sales of Series B Preferred Units between May 2015 and December 31, 2015 to the Series B Preferred and the Series B Warrants based on their relative fair values on the dates of the sales. The difference, for accounting purposes, between the relative fair value per share of the Series B Preferred, approximately $4.12 per share, and its Conversion Price (or stated value) of $7.00 per share represents a deemed dividend to the purchasers of the Series B Preferred Units. Accordingly, we have recognized a deemed dividend in the aggregate amount of $1,811,800 in arriving at net loss attributable to common stockholders for the nine months ended December 31, 2015 in the accompanying Condensed Consolidated Statement of Operations and Comprehensive Loss for the nine months ended December 31, 2015 included elsewhere in this prospectus. Further, we have recognized $1,459,300 representing the 10% cumulative dividend payable on our Series B Preferred as an additional deduction in arriving at net loss attributable to common stockholders for the nine months ended December 31, 2015 in the accompanying Condensed Consolidated Statement of Operations and Comprehensive Loss for the nine months ended December 31, 2015 included elsewhere in this prospectus.

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Liquidity and Capital Resources

Since our inception in May 1998 through December 31, 2015, we have financed our operations through (1) the issuance and sale of our common stock, preferred stock, warrants for common stock, and promissory notes for aggregate cash proceeds of approximately $33.9 million; (2) issuance of common stock and preferred stock with an approximate value at issuance of $28.9 million as consideration for, among other things, technology licenses and patent prosecution, sponsored research, contract research, drug development, drug manufacturing, regulatory services, and legal, investor relations, corporate development and financial advisory services; and (3) receipt of aggregate non-dilutive cash proceeds of approximately $16.4 million from government research and development grant awards and strategic collaboration transactions.

As described more completely in Note 7, Convertible Promissory Notes and other Notes Payable, and Note 8, Capital Stock, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus, between March 31, 2015 and December 31, 2015, we created our Series B 10% Convertible Preferred Stock (Series B Preferred) and eliminated the outstanding balances of approximately $17.2 million of promissory notes, other indebtedness and certain adjustments thereto that was either already due and payable or would have otherwise matured prior to March 31, 2016, through conversion into our Series B Preferred and, with respect to a portion of the indebtedness converted, warrants to purchase common stock. More specifically, through December 31, 2015, we have extinguished and converted (i) all of the Senior Secured Convertible Promissory Notes originally issued to Platinum, (ii) all of the 2014 Unit Notes outstanding at March 31, 2015 and those issued subsequently, and (iii) substantially all other outstanding promissory notes and accounts payable, including those issued to Cato Research Ltd., Cato Holding Company, Morrison & Foerster (Note A and Note B), University Health Network, McCarthy Tetrault, Desjardins Securities, Burr Pilger & Mayer, National Jewish Health, MicroConstants and several others, into an aggregate of 2,618,917 shares of our Series B Preferred. Additionally, through December 31, 2015, in our self-placed private placement of Series B Units, we have sold additional Series B Preferred Units consisting of an aggregate of 628,264 unregistered shares of Series B Preferred and five year warrants to purchase 628,264 shares of our common stock, and we have received cash proceeds of $4,397,800.

At December 31, 2015, we did not have sufficient cash and cash equivalents to enable us to fund our planned operations over the next twelve months, including expected cash expenditures of approximately $6.0 million. In August 2015, we entered into an agreement with Platinum (August 2015 Agreement) pursuant to which we agreed to sell to Platinum an additional $3.0 million of our Series B Preferred and Series B Warrants (collectively, Series B Units). Through December 31, 2015, Platinum purchased an additional $1.65 million of Series B Units under the August 2015 Agreement. Concurrently with its December 2015 purchase of $1.0 million of Series B Units and at our request, Platinum agreed to cancel its right to purchase the remaining $1.35 million of the Series B Units under the August 2015 Agreement. As more particularly disclosed in Note 10, Subsequent Events, to the accompanying Condensed Consolidated Financial Statements for the nine months ended December 31, 2015 included elsewhere in this prospectus, from January 1, 2016 through February 12, 2016, we have sold to certain accredited investors other than Platinum $128,000 of our Series B Units in self-placed private placement transactions. We intend to raise additional capital through conversions, exchanges, issuances, and/or sales of our securities, which may include both debt and equity securities. We may also seek research and development collaborations that could generate revenue, as well as government grant awards. Further, strategic collaborations, such as our February 2015 CRADA with the NIMH providing NIMH funding of our Phase 2a study of AV-101 in MDD, may provide resources to support a portion of our future cash needs and working capital requirements. Although we may seek additional collaborations that could generate revenue, as well as new government grant awards, no assurance can be provided that any such collaborations or awards will occur in the future. Our future working capital requirements will depend on many factors, including, without limitation, the scope and nature of opportunities related to our success and the success of certain other companies in clinical trials, including our development of AV-101 as a treatment for MDD and other CNS conditions, and our stem cell technology platform, the availability of, and our ability to obtain, government grant

awards and our ability to enter into collaborations on terms acceptable to us. To further advance the clinical development of AV-101 and our stem cell technology platform, as well as support our operating activities, we plan to continue to carefully manage our routine operating costs, including the size of our staff and staff salaries and benefits, as well as costs relating to regulatory consulting, contract research and development, investor relations and corporate development, legal, accounting, public company compliance and other professional services and working capital costs.

Notwithstanding the foregoing, substantial additional financing may not be available to us on a timely basis, on acceptable terms, or at all. If we are unable to obtain substantial additional financing on a timely basis in the near term, our business, financial condition, and results of operations may be harmed, the price of our stock may decline, we may be required to reduce, defer, or discontinue certain of our research and development activities and we may not be able to continue as a going concern.

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The following table summarizes changes in cash and cash equivalents for the periods stated (in thousands):

	Nine Months Ended December 31,	
	2015	2014
Net cash used in operating activities	$ (3,499)	$ (1,874)
Net cash used in investing activities	(5)	-
Net cash provided by financing activities	4,592	1,887
Net increase in cash and cash equivalents	1,088	13
Cash and cash equivalents at beginning of period	70	-
Cash and cash equivalents at end of period	$ 1,158	$ 13

Off-Balance Sheet Arrangements

Other than contractual obligations incurred in the normal course of business, we do not have any off-balance sheet financing arrangements or liabilities, guarantee contracts, retained or contingent interests in transferred assets or any obligation arising out of a material variable interest in an unconsolidated entity. VistaGen California has two inactive, wholly owned subsidiaries, Artemis Neuroscience, Inc., a Maryland corporation, and VistaStem Canada, Inc., an Ontario corporation.

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BUSINESS

Overview

We are a clinical-stage biopharmaceutical company dedicated to developing and commercializing innovative product candidates for patients with diseases and disorders involving the central nervous system (CNS). Our lead product candidate, AV-101, is a next generation, orally available prodrug candidate in Phase 2 development, initially for the adjunctive treatment of Major Depressive Disorder (MDD) in patients with an inadequate response to standard antidepressants.

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

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

Currently, we are preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. We anticipate commencement of this potentially pivotal, multi-center, multi-dose, double blind, placebo-controlled Phase 2b efficacy and safety study in the fourth quarter of 2016. Dr. Maurizio Fava, Professor of Psychiatry at Harvard Medical School and Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute and Executive Director, MGH Clinical Trials Network and Institute, will be the principal investigator of our Phase 2b study.

We also believe AV-101 has broad therapeutic utility with multiple near term CNS pipeline expansion opportunities, including chronic neuropathic pain, epilepsy, Huntington's disease and Parkinson's disease.

In addition to clinical development of AV-101, we are also focused on establishing strategic collaborations to advance potential commercial applications of our human pluripotent stem cell (hPSC) technology platform, including drug rescue to develop proprietary new chemical entities (NCEs) for our internal drug candidate pipeline, and regenerative medicine (RM) using blood, cartilage, heart and liver cells derived from our hPSC technology.

AV-101 and Major Depressive Disorder

Background

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

Most standard blockbuster antidepressants target neurotransmitter reuptake inhibition - serotonin (SSRIs) or serotonin/norepinephrine (SNRIs). Even when effective, standard antidepressants take many weeks to achieve adequate therapeutic benefits. Nearly two out of every three drug-treated depression patients, including an estimated 6.9 million drug-treated MDD patients in the U.S., obtain no benefit from initial treatment using standard antidepressants and have significant side effects, including anxiety, metabolic syndrome, sleep disturbance, and sexual dysfunction.

All standard antidepressants have a “Black Box” warning due to safety risks, including, in certain groups, worsening depression and risk of suicide. Unfortunately, even after treatment with as many as four different standard antidepressants, nearly one out of every three drug-treated depression patients do not achieve an adequate therapeutic response, and often transition to using atypical antipsychotics to augment their use of standard antidepressants. However, adjunctive use of atypical antipsychotics increases risk of serious side effects, including tardive dyskinesia, significant weight gain, diabetes and heart disease, while offering only a modest (10% to 20%) potential increase in therapeutic benefit.

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AV-101

AV-101, our orally available prodrug candidate is in Phase 2 clinical development for the adjunctive treatment of MDD patients with an inadequate response to standard antidepressants. As published in the October 2015 issue of the peer-reviewed, Journal of Pharmacology and Experimental Therapeutics, in an article entitled, The prodrug 4-chlorokynurenine causes ketamine-like antidepressant effects, but not side effects, by NMDA/glycineB-site inhibition, using well-established preclinical models of depression, AV-101 was shown to induce fast-acting, dose-dependent, persistent and statistically significant antidepressant-like responses, following a single treatment. These responses were equivalent to those seen with a single, sub-anesthetic control dose of the NMDAR antagonist ketamine. In the same preclinical studies, the SSRI fluoxetine did not induce rapid onset antidepressant-like responses.

Following the completion of our randomized, double blind, placebo-controlled Phase 1a and Phase 1b safety studies funded by the NIH, we are now collaborating with the NIMH under our February 2015 CRADA. Pursuant to the CRADA, the NIMH is sponsoring our ongoing Phase 2a efficacy and safety study of AV-101 in subjects with treatment-resistant MDD. The Principal Investigator of our Phase 2a study is Dr. Carlos Zarate, Jr. of the NIMH. The trial is expected to enroll 24 to 28 patients, and the first patient was dosed in November 2015. We currently anticipate receiving topline results of our Phase 2a study in the second quarter of 2017.

We are preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. We anticipate the launch of this study, which is expected to enroll approximately 315 patients, and seek FDA Fast Track designation for AV-101 in the fourth quarter of 2016. The Principal Investigator of this Phase 2b study will be Dr. Maurizio Fava of Harvard Medical School. We anticipate top line results from our Phase 2b study in the second quarter of 2018, and, although no assurances can be given, we estimate that AV-101 may be ready for commercialization as early as 2021. We intend to seek FDA Fast Track designation for AV-101 in MDD and anticipate that such designation may be granted in the fourth quarter of 2016.

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

CardioSafe 3D™; NCE Drug Rescue and Regenerative Medicine (RM)

CardioSafe 3D™ is our customized in vitro cardiac bioassay system capable of predicting potential human heart toxicity of NCEs in vitro, long before they are ever tested in animal and human studies. Our current strategic interests involving CardioSafe 3D and our stem cell technology platform include establishing collaborative arrangements focused on advancing potential commercial applications, including both (i) drug rescue designed to expand our pipeline by leveraging substantial prior investments by pharmaceutical companies and others related to screening large-scale compound libraries, and optimizing and testing for efficacy NCEs terminated before FDA approval due to heart toxicity risks and (ii) RM involving hPSC-derived blood, bone, cartilage, heart and/or liver cells.

Our Strategy

Our core strategy is to develop, and commercialize innovative small molecule drugs that address significant unmet medical needs related to CNS diseases and disorders. 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 and regulatory experience to lead and execute the development and commercialization of our CNS product candidate 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. Under our 2015 CRADA with the NIMH, we launched our ongoing NIMH-sponsored AV-101 MDD Phase 2a clinical study in collaboration with Dr. Carlos Zarate of the NIMH. This study was initiated in October 2015, and the first patient in the study was dosed in November 2015. We are currently preparing to launch our potentially pivotal, multi-center Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. We intend to develop AV-101 internally, through a pivotal Phase 3 clinical study and submission of our New Drug Application (NDA) to the FDA. 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 standard antidepressants and atypical antipsychotics or (B) collaborating with a pharmaceutical company with a strong commercial presence in U.S. depression and other CNS markets. Outside the U.S., we intend to commercialize AV-101 by establishing a partnering arrangement with one or more pharmaceutical companies with extensive commercial capabilities in multiple non-U.S. depression and other CNS markets.

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

Capitalize on our drug rescue and RM opportunities using our stem cell technology. We are using our stem cell technology and proprietary cardiac bioassay system, CardioSafe 3D, to screen and develop proprietary NCEs through drug rescue programs intended to produce proprietary NCEs for our internal drug development pipeline, without incurring many of the substantial costs and risks typically inherent in new drug discovery and nonclinical drug development. In order to capitalize on our existing stem cell technology, we are focused on establishing new strategic collaborations, including investigating potential spin-off opportunities. As most of our resources are currently focused on the clinical development of AV-101, a strategic collaboration or spin-off would allow us to capitalize on our existing stem cell technology and shift our focus exclusively to developing our CNS pipeline.

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

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

Our Product Opportunities

AV-101 (L-4-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 into its active metabolite, 7-chlorokynurenic acid (7-Cl-KYNA), a well-characterized, potent and highly selective antagonist of then NMDAR at the GlyB co-agonist site.

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

Major Depressive Disorder

Depression is a serious medical illness and a global public health concern. The WHO estimates that depression is the leading cause of disability worldwide, and is a major contributor to the global burden of disease, affecting 350 million people globally. According to the CDC, approximately one in every 10 Americans aged 12 and over takes antidepressant medication.

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% individuals with MDD.

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Standard Antidepressants

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

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 NIMH, 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 low dose of ketamine (0.5 mg/kg over 40 minutes) produced robust and rapid antidepressant effects in MDD patients who had not responded to standard anti-depressants. These results were in contrast to the very slow onset of SSRIs and SNRIs that usually require many weeks or months of chronic usage to achieve similar antidepressant effects. The potential for widespread therapeutic use of current FDA-approved ketamine, a Schedule III drug, for MDD is limited by its potential for abuse, dissociative and psychosis-like side effects and by practical challenges associated with the necessity of I.V. administration in a medical center. Notwithstanding these limitations, however, the discovery of ketamine's fast-acting antidepressant effects revolutionized thinking about the current MDD treatment paradigm and increased interest in the development of a new generation of antidepressants with a fast-acting mechanism of action similar to ketamine's. Our orally available AV-101 is among the next generation of antidepressants with potential to deliver fast-onset ketamine-like antidepressant effects, without ketamine's side effects or required I.V. administration in a medical setting.

AV-101 and Major Depressive Disorder

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

AV-101's mechanism of action is fundamentally differentiated from all standard antidepressants and all atypical antipsychotics often used to augment inadequate response with standard antidepressants, placing it among a new generation of glutamatergic antidepressants with potential to treat millions of MDD sufferers worldwide who are poorly served by SSRIs, SNRIs and other current depression therapies. AV-101 is functionally similar to ketamine in that both induce antidepressant activity via glutamatergic activation involving AMPA receptor pathways. However, AV-101 down-regulates the NMDAR channel activity, whereas ketamine blocks it. AV-101, as a prodrug, produces in the brain an antagonist that down-regulates the NMDAR by selectively binding to the functionally required GlyB site

of the NMDAR. Strong experimental evidence confirms that down-regulating the NMDAR by targeting the GlyB site can produce potent antidepressive effects and bypass adverse effects that result when ketamine blocks the NMDA ion channel. Experimental evidence supports the conclusion that this NMDAR modulation by AV-101 may then result in a glutamatergic activation that depends on the AMPA receptor pathway, resulting in an increase in neuronal connections that has been associated with the fast-acting antidepressant effects similar to those seen with ketamine.

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

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Building on over $8.8 million of prior grant award funding from the NIH for preclinical and Phase 1 clinical development of AV-101, in February 2015, we entered into our CRADA with the NIMH. Under the CRADA, we are collaborating with Dr. Carlos Zarate and the NIMH on a Phase 2a clinical study of AV-101 in subjects with treatment-resistant MDD. Pursuant to the CRADA, this study is being conducted at the NIMH by Dr. Zarate and being fully-sponsored by the NIMH. The primary objective of the NIH-funded Phase 2a study will be to evaluate the ability of AV-101 to improve overall depressive 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. The first patient in this Phase 2a study was dosed in November 2015. We anticipate top line results in this study in the second quarter of 2017.

We are currently preparing to launch our Phase 2b clinical study of AV-101 for the adjunctive treatment of MDD in patients with an inadequate response to standard antidepressants. We anticipate the launch of this potentially pivotal multi-center, multi-dose, double blind, placebo-controlled Phase 2b efficacy and safety study, which is expected to enroll approximately 315 patients, in the fourth quarter of 2016. The Principal Investigator of the study will be Dr. Maurizio Fava of Harvard Medical School. Dr. Fava was the co-Principal Investigator with Dr. A. John Rush of the largest clinical trial ever conducted in depression, STAR*D, whose findings were published in journals such the New England Journal of Medicine (NEJM) and the Journal of the American Medical Association (JAMA). We anticipate top line results in this study in the second quarter of 2018.

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

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

Chronic Neuropathic Pain and Acute Tissue Injury Hyperalgesia

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

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

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

For the carrageenan inflammatory thermal hyperalgesia model, neither MK-801, gabapentin, nor AV-101 had an effect on acute thermal nociception, but produced a dose dependent block of the carrageenan-induced hyperalgesia

that were greater than 2 SD of the vehicle: There were no behavioral changes observed at any AV-101 dose, but signs of behavioral and motor dysfunction were observed for gabapentin and MK-801 treated animals. The profile of analgesic activity observed for AV-101 in the formalin and inflammatory thermal hyperalgesia model systems supports the conclusion that AV-101 demonstrates anti-hyperalgesia activity in validated models of facilitated pain processing produced by peripheral tissue inflammation.

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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.

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) is an inherited disorder that causes degeneration of brain cells, called neurons, in motor control regions of the brain, as well as other areas. Symptoms of the disease, which gets progressively worse, include uncontrolled movements (called chorea), abnormal body postures, and changes in behavior, emotion, judgment, and cognition. HD is caused by an expansion in the number of glutamine repeats beyond 35 at the amino terminal end of a protein termed “huntingtin.” Such a mutation in huntingtin leads to a sequence of progressive cellular changes in the brain that result in neuronal loss and other characteristic neuropathological features of HD. These are most prominent in the neostriatum and in the cerebral cortex, but also observed in other brain areas.

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

Based on the hypothesis that 3-HK and QUIN are involved in the progression of HD, early intervention aimed at affecting the kynurenine pathway in the brain may present a promising treatment strategy. We believe the ability of AV-101 to reduce the brain levels of neurotoxic OUIN and to potentially produce significant local concentrations of 7-Cl-KYNA on chronic administration, presents an exciting opportunity for Phase 2 clinical investigation of AV-101 as a potential chronic treatment of the symptoms 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 [Tmax], approximately 0.25 to 0.5 hours), adequate bioavailability (rats: approximately 39% to 94%), and plasma elimination half-life (rats: t1/2 approximately 1 to 3 hours). Furthermore, in rats 7-Cl-KYNA was detected in the plasma and reached the maximum plasma concentration (Cmax) approximately 0.25 to 0.5 hours after oral administration, suggesting a rapid conversion of AV-101 to 7-Cl-KYNA. Pharmacokinetic 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 Cmax values increased non-proportionately with dose level in dogs, AUC values only marginally increased with dose in monkeys, with little change in Cmax values.

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.

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.

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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 4-Cl-KYN or 7-Cl-KYNA. Primary pharmacodynamic studies conducted in rodent models for neuropathic pain demonstrated AV-101's antihyperalgesic activity in models of facilitated pain processing, its analgesic properties, its ability to provide neuroprotection from excitotoxic death, its ability to reduce seizures, and its activity in multiple preclinical models of depression.

Nonclinical Absorption, Distribution, Metabolism and Excretion Studies

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

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

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

Nonclinical Toxicology Studies

The safety profile of AV-101 was determined in single-dose, range-finding, and repeated-dose toxicology studies in rats and dogs, and in a single-dose study in monkeys. A GLP CNS safety pharmacology study in rats that included a microscopic evaluation for Olney lesions was also conducted. Additionally, pivotal GLP 14-day repeated-dose

toxicology studies in rats and dogs have been conducted. The genotoxic potentials of AV-101 and 7-Cl-KYNA were assessed in multiple in vitro and in vivo genotoxicity studies, including bacterial reverse mutation, chromosomal aberration, mouse lymphoma TK+/-, and micronucleus tests. Neither was determined to be mutagenic.

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

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

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AV-101 Phase 1 Clinical Safety Studies

Summary

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

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/54) of the subjects receiving AV-101 and 0% of the 30 subjects receiving placebo reported “feelings of well-being” (coded as euphoric mood), similar to the fast-acting antidepressant effects reported in the literature with ketamine.

Phase 1a Study

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

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

Phase 1a Study Pharmacokinetics Summary

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

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

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

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

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

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

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Assessment of Dose Proportionality

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

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

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

Phase 1a Safety Summary

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

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

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Phase 1b Study

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

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

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

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

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

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

A total of 40 AEs were reported by 24 of 37 (64.9%) subjects receiving AV-101, and 17 AEs were reported by 10 of 13 (76.9%) subject receiving placebo (Table 2). The frequency of AEs was similar among the treatment groups. Thirty-four subjects experienced a total of 57 AEs, with 16 (28.1% of the total AEs) in the 360-mg group, 14 (24.6% of the total AEs) in the 1,040-mg group, 10 (17.5% of the total AEs) in the 1,440-mg group, and 17 (29.8% of the total AEs) in the placebo group. All of the AEs were completely resolved, and no SAEs were reported.

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

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

The determination of the relationship of the AE to the study drug was made when the data were unblinded. Ten of the 15 AEs (66.7%) that occurred in the 360-mg AV-101 group, 10 of the 14 AEs (71.4%) that occurred in the 1,040-mg AV-101 group, 7 of the 10 AEs (70.0%) that occurred in the 1,440-mg AV-101 group, and 13 of the 17 AEs (76.5%) that occurred in the placebo group were determined to be possibly related to study drug. One (5.9%) AE in the placebo group was probably related to study drug (rash around neck). Of the 57 reported AEs, 49 (85.9%) were of mild intensity and 8 (14.0%) were of moderate intensity. There were 2 moderate intensity AEs in the 360-mg AV-101 group; 1 was unrelated pain in the right foot, and 1 was a possibly related headache. All other moderate AEs occurred in the placebo group and included nausea or vomiting (2 AEs), headache (2 AEs), and rash around the neck (1 AE). No SAEs were reported.

Even though these safety studies were not designed to quantitatively assess effects on mood, during the interviews 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 Cmax, Tmax, AUC0-t, AUC0- , and t1/2.

Plasma concentration-time profiles obtained for 4-Cl-KYN after administration of once-daily oral doses of 360, 1,080, or 1,440 mg AV-101 were consistent with rapid absorption of the oral dose and first-order elimination of both 4-Cl-KYN and 7-Cl-KYNA, with evidence of multicompartment kinetics, particularly for the metabolite 7-Cl-KYNA. Several subjects had plasma concentration-time profiles with a last measurable sample that appeared to be an outlier or suggested multicompartment kinetics, making it challenging to identify a terminal log-linear elimination phase. Particularly for 7-Cl-KYNA, using the last two measurable samples to calculate t1/2 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 t1/2 and to report a meaningful value, the final three samples with measurable concentrations were used to calculate t1/2 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 t1/2 (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. ≥ 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.

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Phase 1 Program - Summary

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

Although the Phase 1 safety and pharmacokinetic studies were not designed to measure or evaluate the potential antidepressant effects of AV-101, approximately 9% (5/54) of the subjects receiving AV-101 and 0% of the 30 subjects receiving placebo reported “feelings of well-being” (coded as euphoric mood), similar to the fast-acting antidepressant effects reported in the literature with ketamine.

The five reports of feelings of well being occurred in one subject each at 360 (7%, 1 of 15 subjects) and 1,080 mg (7%, 1 of 15 subjects), and three subjects at 1,440 mg (20%, 3 of 15 subjects) in the Phase 1a and Phase 1b clinical studies, combined. Four of the five subjects reporting feelings of well-being did not have any other adverse experiences, and one subject (1,080 mg) also reported a mild headache. These results suggest a dose response and that AV-101 at the higher doses may lead to an increased positive mood.

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Stem Cell Technology

Overview

Our stem cell technology platform is based on proprietary and licensed technologies for controlling the differentiation of human pluripotent stem cells (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 used our hPSC-derived cardiomyocytes (human heart cells) in CardioSafe 3D™, our novel, customized in vitro bioassay system for predicting potential cardiotoxicity of 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, and that CardioSafe 3D offers us a new paradigm for evaluating and predicting potential heart toxicity of 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 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 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.

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.

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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.

Because they can significantly affect the therapeutic and/or toxic effects of drugs, these genetic variations have an impact on drug discovery and development. We believe iPSC technologies may allow the rapid and efficient generation of hPSCs from individuals with specific genetic variations. These hPSCs might then be used to produce cells to model specific diseases and genetic conditions for drug discovery and drug rescue purposes.

Medicinal Chemistry

Medicinal chemistry involves designing, synthesizing, or modifying a small molecule compound or drug suitable for clinical development. It is a highly interdisciplinary science combining organic chemistry, biochemistry, physical chemistry, computational chemistry, pharmacology, and statistics. The combination of medicinal chemistry with the proprietary and licensed hPSC technologies underlying our stem cell technology platform are core components of our drug rescue business model.

CardioSafe 3D

The limitations of current preclinical drug testing systems used by pharmaceutical companies and others contribute to the high failure rate of NCEs. Incorporating novel in vitro assays using hPSC-derived cardiomyocytes (hPSC-CMs) early in preclinical development offers the potential to improve clinical predictability, decrease development costs, and avoid adverse patient effects, late-stage clinical termination, and product recall from the market.

We produce fully functional, non-transformed hPSC-CMs at a level of purity greater than 95% and with normal ratios of all important cardiac cell types. Importantly, our hPSC-CM differentiation protocols do not involve either genetic modification or antibiotic selection. This is important because genetic modification and antibiotic selection can distort the ratio of cardiac cell types and have a direct impact on the ultimate results and clinical predictivity of assays that incorporate hPSC-CMs produced in such a manner. In addition to normal expression all of the key ion channels of the human heart (calcium, potassium and sodium) and various cardiomyocytic markers of the human heart, our

CardioSafe 3D cardiac toxicity assays screening for both direct cardiomyocyte cytotoxicity and arrhythmogenesis (or development of irregular beating patterns). We believe CardioSafe 3D is sensitive, stable, reproducible and capable of generating data enabling a more accurate prediction of the in vivo cardiac effects of NCEs than is possible with existing preclinical testing systems, particularly the hERG assay.

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Limited Clinical Predictivity of the FDA-Required hERG Assay

The hERG assay, which uses either transformed hamster ovary cells or human kidney cells, is currently the only in vitro cardiac safety assay required by FDA Guidelines (ICH57B). We believe the clinical predictivity of the hERG assay is limited because it assesses only a single cardiac ion channel - the hERG potassium ion channel. It does not assess any other clinically relevant cardiac ion channels, including calcium, non-hERG potassium and sodium ion channels. Also, importantly, the hERG assay does not assess the normal interaction between these ion channels and their regulators. In addition, the hERG assay does not assess clinically relevant cardiac biological effects associated with cardiomyocyte viability, including apoptosis and other forms of cytotoxicity, as well as energy, mitochondria and oxidative stress. As a result of its limitations, results of the hERG assay can lead to false negative and false positive predictions regarding the cardiac safety of new drug candidates.

Broad Clinical Predictivity of CardioSafe 3D

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

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

These five CardioSafe 3D biological assays were correlated to reported clinical results using reference compounds known to be cardiotoxic in humans versus compounds known to be safe in humans. These reference compounds were representative of eight different drug classes, including:

1. ion channel blockers: amiodarone, nifedipine;
2. hERG trafficking blockers: pentamidine, amoxapine;
3. -1 adrenoreceptors: doxazosin;
4. protein and DNA synthesis inhibitors: emetine;
5. DNA intercalating agents: doxorubicin;
6. antibiotics: ampicillin, cefazolin;
7. NSAID: aspirin; and
8. kinase inhibitors: staurosporine.

This suite of five CardioSafe 3D cytotoxicity assays provided measurement of cardiac drug effects with high sensitivity that are consistent with the expected cardiac responses to each of these compounds. Based on our results, we believe CardioSafe 3D provides valuable and far more comprehensive bioanalytical tools for both assessing the effects of pharmaceutical compounds on cardiac cytotoxicity than the hERG assay and can elucidate for us and our medicinal chemistry partner specific mechanisms of cardiac toxicity, thereby laying what we believe is a novel and advantageous foundation for our CardioSafe 3D drug rescue programs.

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

1. One FDA-approved drug (aspirin) without cardiac liability to serve as a negative control;
2. Five FDA-approved drugs (astemizole, sotalol, cisapride, terfenadine and sertindole) that were withdrawn from the market due to heart toxicity concerns;
3. Five FDA-approved drugs (fexofenadine, nifedipine, verapamil, lidocaine and propranolol) that have certain measurable non-toxic cardiac effects consistent with clinical experience with such compounds. Note: fexofenadine is a non-cardiotoxic drug variant of terfenadine; and
4. One research compound (E-4031) failed in Phase 1 human clinical study before being discontinued due to inducing heart arrhythmias.

We have validated that CardioSafe 3D is capable of assessing important electrophysiological activity of drugs or new drug candidates, including spike amplitude, beat period and field potential duration. Our CardioSafe 3D MEA assay, which we refer to as ECG in a test tube™, was reproducible and consistent with the known human cardiac effects of all twelve compounds studied, based on the mechanisms of action and dosage of the compounds. For instance, by using CardioSafe 3D, we were able to distinguish between the arrhythmogenic cardiac effects of terfenadine (Seldane™), withdrawn by the FDA due to cardiotoxicity, and the cardiac effects of the closely structurally-related compound, fexofenadine (Allegra™), a safe variant of terfenadine, which remains on the market. We believe our correlation data demonstrate that CardioSafe 3Dprovides valuable and more comprehensive bioanalytical tools for in vitro cardiac safety screening than the hERG assay. We believe CardioSafe 3D will contribute to our efficient and rapid identification of novel, potentially safer proprietary NCEs in our drug rescue programs.

CardioSafe 3D, Going Far Beyond the hERG Assay

The table below reflects the broad cardiotoxicity screening capabilities CardioSafe 3D, which we believe go far beyond what is possible to assess in vitro using the FDA-required hERG assay:

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

Using Stem Cell Technology to Produce and Develop Drug Rescue NCEs

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

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

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

Strategic Development and Commercialization of Drug Rescue NCEs

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

Regenerative Medicine

Although we believe the best and most valuable near term commercial application of our stem cell technology platform is for small molecule drug rescue, we also believe stem cell technology-based RM has the potential to transform healthcare in the U.S. over the next decade by providing new approaches for treating the fundamental mechanisms of disease. We currently intend to establish strategic collaborations to leverage our stem cell technology platform, our expertise in human biology, differentiation of human pluripotent stem cells to develop functional adult human cells and tissues involved in human disease, including blood, bone, cartilage, heart and liver cells, and our expertise in designing and developing novel, customized biological assay systems with the cells we produce, for regenerative medicine purposes, including developing novel human disease models for discovery of small molecule drugs with regenerative and therapeutic potential. Among our key objectives will be to establish one or more strategic collaborations designed to assess our RM opportunities through exploratory nonclinical POC studies.

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Strategic Transactions and Relationships

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

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

- contract medicinal chemistry companies, such as Synterys, Inc., to design, produce and analyze potential drug rescue NCEs; and

- contract clinical development and regulatory organizations (CROs), such as Cato Research, Ltd. and PPD, for regulatory expertise and clinical development support.

Cato Research

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

Cato BioVentures

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

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

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Cardiac Safety Research Consortium

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

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

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

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

Centre for Commercialization of Regenerative Medicine

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

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

Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI)

Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI) is an academic CRO, part of the Department of Psychiatry of the Massachusetts General Hospital (MGH), a leader in academic scientific and clinical research in psychiatry. By exploring the brain science, genetics, and neurobiology of psychiatric disorders, the MGH CTNI has been instrumental in the development of novel treatments and surrogate markers of illness and therapeutic

response. Its scientific and clinical research has been instrumental in defining the standards for the state-of-the-art practice of psychiatry. We are working with MGH CTNI, including its principals, Dr. Maurizio Fava and Dr. Thomas Laughren, in connection with the planning and execution of our potentially pivotal Phase 2b clinical study of AV-101 for treatment of MDD. Dr. Fava is acknowledged as a world renowned expert in depressive disorders and psychopharmacology. He is Director of the Division of Clinical Research of the MGH Research Institute, Executive Vice Chair, Department of Psychiatry, at MGH, and Executive Director of MGH CTNI. He will serve as Principal Investigator of Phase 2b study of AV-101 in MDD. Dr. Laughren is the former FDA Division Director, Division of Psychiatry Products, Center for Drug Evaluation and Research (CDER).

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PPD

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

Synterys, Inc.

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

United States National Institutes of Health

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

United States National Institute of Mental Health

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

University Health Network, McEwen Centre for Regenerative Medicine

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

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

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

Intellectual Property

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

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

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

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AV-101

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

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

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

Presently, we are prosecuting one family of patent applications in the USPTO, European Patent Office and selected major markets related to specific dosage formulations of AV-101, as well as to methods of treating depression, hyperalgesia pain and several other neurological conditions. For reference, these are based on PCT patent application WO2014/116739. We have recently filed a continuation application in this family in the U.S., focused on the treatment of depression, and are seeking accelerated examination for this application. It is likely that we will receive a substantive response from the USPTO by the end of 2016. There is no guarantee, however, that the USPTO will allow any of the pending claims.

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

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

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

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

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

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

Stem Cell Technology

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

Overall, our stem cell patent portfolio includes nine patent families, which collectively include 14 issued U.S. patents that remain in force as well as several foreign counterpart patents in countries of commercial interest to VistaGen. The portfolio also includes several patent applications pending in the U.S. and in various foreign countries. For reference, our stem cell patent portfolio is based on PCT patent applications WO 1997/021802, WO2000/034525, WO2004/098490, WO2001/096866, WO2012/024782, WO2013/075222, WO2014/124527, WO2014/161075 and WO2015035506, several of which are discussed below.

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

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

Trademarks

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

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Sponsored Research Collaborations and Intellectual Property Rights

University Health Network, McEwen Centre for Regenerative Medicine, Toronto, Ontario

Our strategic relationship with our co-founder, Dr. Gordon Keller, Director of the UHN's McEwen Centre, is focused on, among other things, developing improved methods for differentiation of cardiomyocytes (heart cells) from hPSCs, and their uses in bioassay systems for drug discovery and drug development, including drug rescue. Pursuant to our sponsored research collaboration agreement with UHN, we have acquired exclusive worldwide rights to patent applications in the U.S. and foreign countries on multiple inventions arising from studies we have sponsored, under pre-negotiated license terms. Such pre-negotiated terms provide for royalty payments based on product sales that incorporate the licensed technology and milestone payments based on the achievement of certain events. Any drug rescue NCEs that we develop will not incorporate the licensed technology and, therefore, will not require any royalty payments. To the extent we incur royalty payment obligations from other business activities, the royalty payments will be subject to anti-stacking provisions, which reduce our payments by a percentage of any royalty payments paid to third parties who have licensed necessary intellectual property to us. These licenses will remain in force for so long as we have an obligation to make royalty or milestone payments to UHN, but may be terminated earlier upon mutual consent, by us at any time, or by UHN for our breach of any material provision of the license agreement that is not cured within 90 days.

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

UHN Licenses for Stem Cell Culture Technology

In October 2011, we licensed stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. This exclusive license conveyed rights to a patent application entitled "Methods for enriching pluripotent stem cell derived cardiomyocyte progenitor cells and cardiomyocyte (heart) cells based on SIRPA expression" covered by PCT patent application WO/2012/024782, and any related patent application claiming priority from these. This technology involves a heretofore unknown cell surface protein, SIRPA (signal-regulatory protein alpha) that is expressed by early immature precursors for cardiomyocytes. Antibodies specific to SIRPA allow the identification and enrichment of these early cardiomyocyte precursors, which we believe will provide benefits in terms of purity, functionality and reproducibility for not only CardioSafe 3D in vitro safety assays for drug screening and development, but also potentially for production of cardiomyocytes for cell therapy and regenerative medicine applications.

In April 2012, we licensed stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. The licensed technology may be used to develop hematopoietic precursor stem cells from human pluripotent stem cells, with the goal of developing drug discovery screening and regenerative medicine applications for human blood system disorders. This technology is covered by PCT patent application WO/2013/075222, and any related patent application claiming priority from these. We believe this stem cell technology dramatically advances our ability to produce and purify this important blood stem cell precursor for both in vitro drug discovery screening and potential regenerative medicine applications. In addition to defining new cell culture methods for our use, the technology describes the surface characteristics of stem cell-derived adult hematopoietic stem cells. Most groups study embryonic blood development from stem cells, but we are able to not only purify the stem cell-derived precursor of all adult hematopoietic cells, but also pinpoint the precise timing when adult blood cell differentiation takes place in these

cultures. We believe these early cells have the potential to be the precursors of the ultimate adult, bone marrow-repopulating hematopoietic stem cells to repopulate the blood and immune system when transplanted into patients prepared for bone marrow transplantation. These cells have important potential therapeutic applications for the restoration of healthy blood and immune systems in individuals undergoing transplantation therapies for cancer, organ grafts, HIV infections or for acquired or genetic blood and immune deficiencies.

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In December 2014, we licensed stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. This exclusive license conveyed rights to a patent application entitled "Methods for generating hepatocytes and cholangiocytes from pluripotent stem cells" covered by PCT patent application WO/2014/124527, and any future patent application claiming priority from it. The licensed technology describes advanced methods for the production of mature hepatocytes and cholangiocytes, the primary cell types of the liver. The liver plays an important role in many bodily functions including protein production, blood clotting, as well as glucose, iron and lipid metabolism. Hepatocytes are the major cells responsible for metabolizing drugs, drug-drug interactions, and are the target for a variety of liver diseases including drug-induced liver failure, Cirrhosis, and viral infections. Cholangiocytes are the precursors for the biliary system found in the liver, i.e. bile ducts and gallbladder. The biliary system is a significant target for many conditions, including drug toxicities, cholecystitis, and liver-related abnormal function associated with the cystic fibrosis mutation. The licensed technology now enables us to more efficiently produce, human hepatocytes and cholangiocytes with more adult-like functions for in vitro drug discovery and LiverSafe 3D toxicity assays to support our drug rescue programs, as well as the therapeutic potential for cell-based therapies.

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

In December 2014, we licensed stem cell culture technology from UHN's McEwen Centre pursuant to the SCRA. This exclusive license conveyed rights to patent application entitled "Methods and compositions for generating chondrocyte lineage cells and/or cartilage like tissue" covered by PCT patent application WO/2014/161075 application, and any future patent application claiming priority from it. There are two types of chondrocytes, "articular" and "growth plate". Articular chondrocytes are responsible for cartilage that lines our joints, whereas growth plate chondrocytes are involved with new bone formation. Osteoarthritis is debilitating joint diseases resulting from the degeneration of articular cartilage leading to inappropriate bone development (spurs) in the joint. These technologies will allow us to develop in vitro assays to study the process of the degeneration of articular cartilage, and provides novel tools for testing drugs that have the potential to reduce this degeneration. These cells also provide the necessary cells for developing cell therapy approaches for treating osteoarthritis.

U.S. Government Rights

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

Competition

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

Currently, there are no FDA-approved therapies for MDD with the mechanism of action of AV-101. However, products approved for other indications, for example, 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 psychotherapy and electroconvulsive therapy, are sometimes used instead of and before antidepressant medications to treat patients with MDD.

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In the field of new generation antidepressants focused on modulation of the NMDAR, our principal competitor is Naurex, Inc., which is developing rapastinel (formerly GLYX-13) and NRX-1074 for treatment-resistant MDD. In August, 2015, Allergan plc., a global pharmaceutical company, acquired rapastinel and NRX-1074 from Naurex, Inc. for a $560 million up front payment in cash, as well as substantial potential research and development success-based and sales threshold milestone payments. Although each of these drug candidates is a peptide and may not be orally active (rapastinel is only administered intravenously and, we believe, NRX-1074 has not yet been administered orally to patients), both are new generation NMDAR modulators focused on the GlyB site of the NMDAR.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of treatments and the commercialization of those treatments. We believe that a range of pharmaceutical companies have programs to develop small molecule drug candidates for the treatment of depression, including MDD, epilepsy, neuropathic pain, Parkinson's disease and other neurological conditions and diseases, including, but not limited to, Abbott Laboratories, Allergan, AstraZeneca, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Roche, Sanofi, Shire, 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 expect that AV-101 will have to compete with a variety of therapeutic products and procedures.

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

Government Regulation

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

authority, submitted for review and approved by the regulatory authority.

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U.S. Drug Development

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

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

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

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

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

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

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

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

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

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

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

The non-clinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. Non-clinical tests include laboratory evaluation of product chemistry, formulation, stability and toxicity, as well as animal studies to assess the characteristics and potential safety and efficacy of the product.

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

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

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

Clinical Trials

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

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

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

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

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

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

NDA and FDA Review Process

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

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

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

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

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

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

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-marketing testing or clinical trials and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess a drug's safety and efficacy and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a risk evaluation and mitigation strategy (REMS) to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the

NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

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Orphan Drug Designation

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

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

Expedited Development and Review Programs

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

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

distribution or use is restricted, it will require such post-marketing restrictions, as it deems necessary to assure safe use of the drug, such as:

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

distribution conditioned on the performance of specified medical procedures.

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

Pediatric Trials

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

Post-Marketing Requirements

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

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

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

Other Regulatory Matters

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

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

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

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

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

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

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product

development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

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Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application (ANDA) or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the non-clinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued “Written Request” for such a trial.

European Union Drug Development

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

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

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

European Union Drug Review and Approval

In the European Economic Area (EEA) (which is comprised of the 27 Member States of the European Union (excluding Croatia) plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after

obtaining a Marketing Authorization, (MA). There are two types of marketing authorizations:

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

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

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

European Union New Chemical Entity Exclusivity

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

European Union Orphan Designation and Exclusivity

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

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

Rest of the World Regulation

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

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

Reimbursement

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

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

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the MMA) established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products

covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

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

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

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

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

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Stem Cell Technology - United States

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

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

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

Stem Cell Technology - Canada

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

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

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

Subsidiaries and Inter-Corporate Relationships

VistaGen Therapeutics. Inc., a California corporation, is our wholly-owned subsidiary and has the following two wholly-owned subsidiaries: VistaStem Canada Inc., a corporation incorporated pursuant to the laws of the Province of

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

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Employees

As of May 6, 2016, we employed eight full-time employees, three of whom have doctorate degrees. Five full-time employees work in research and development and laboratory support services and three full-time employees work in general and administrative roles. Staffing for all other functional areas is achieved through strategic relationships with service providers and consultants, each of whom provides services on a real-time, as-needed basis, including human resources and payroll, information technology, facilities, legal, stock plan administration, investor relations and website maintenance, regulatory affairs, and FDA program management.

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

Facilities

We lease our office and laboratory space, which consists of approximately 10,000 square feet located in South San Francisco, California. Our lease expires on July 31, 2017.

Legal Proceedings

As of the date of this prospectus, we were not party to any legal matters or claims. In the future, we may become party to legal matters and claims arising in the ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our results of operations.

Environmental Regulation

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

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DIRECTORS AND EXECUTIVE OFFICERS

Our senior management is composed of individuals with significant management experience. Our directors and executive officers are as follows:

Name	Age	Position
Shawn K. Singh	53	Chief Executive Officer and Director
H. Ralph Snodgrass, Ph.D.	66	Founder, President, Chief Scientific Officer and Director
Jerrold D. Dotson	62	Vice President, Chief Financial Officer and Secretary
Jon S. Saxe (1)	79	Director
Brian J. Underdown, PhD. (2)	75	Director
Jerry B. Gin, Ph.D, MBA (3)	72	Director

(1) Chairman of the audit committee and member of the compensation committee and corporate governance and nominating committee.
(2) Member of the audit committee and chairman of the compensation committee and corporate governance and nominating committee.
(3) Member of the audit committee.

Executive Officers

Shawn K. Singh has served as our Chief Executive Officer since August 2009; he joined our Board of Directors in 2000 and served on our management team (part-time) from late-2003, following our acquisition of Artemis Neuroscience, of which he was President, to August 2009. Mr. Singh has over 25 years of experience working with biotechnology, medical device and pharmaceutical companies, both private and public. From February 2001 to August 2009, Mr. Singh served as Managing Principal of Cato BioVentures, a life science venture capital firm, and as Chief Business Officer and General Counsel of Cato Research Ltd, a profitable global contract research organization (CRO) affiliated with Cato BioVentures. Mr. Singh served as President (part-time) of Echo Therapeutics (NASDAQ: ECTE), a medical device company developing a non-invasive, wireless continuous glucose monitoring (CGM) system, from September 2007 to June 2009, and as a member of its Board of Directors from September 2007 through December 2011. He also served as Chief Executive Officer (part-time) of Hemodynamic Therapeutics, a private biopharmaceutical company affiliated with Cato BioVentures, from November 2004 to August 2009. From late-2000 to February 2001, Mr. Singh served as Managing Director of Start-Up Law, a management consulting firm serving biotechnology companies. Mr. Singh also served as Chief Business Officer of SciClone Pharmaceuticals (NASDAQ: SCLN), a revenue-generating, specialty pharmaceutical company with a substantial commercial business in China and a product portfolio spanning major therapeutics markets, including oncology, infectious diseases and cardiovascular disorders, from late-1993 to late-2000, and as a corporate finance associate of Morrison & Foerster LLP, an international law firm, from 1991 to late-1993. Mr. Singh currently serves as a member of the Board of Directors of Armour Therapeutics, a private biotechnology company focused on prostate cancer. Mr. Singh earned a B.A. degree, with honors, from the University of California, Berkeley, and a Juris Doctor degree from the University of Maryland School of Law. Mr. Singh is a member of the State Bar of California.

We selected Mr. Singh to serve on our Board of Directors due to his substantial practical experience and expertise in senior leadership roles with multiple private and public biotechnology, pharmaceutical and medical device companies, and his extensive experience in corporate finance, venture capital, corporate governance and strategic partnering.

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H. Ralph Snodgrass, Ph.D. co-founded VistaGen with Dr. Gordon Keller in 1998 and served as our Chief Executive Officer until August 2009. Dr. Snodgrass has served as our President and Chief Scientific Officer since August 2009. He has served as a member of our Board of Directors since 1998. Prior to founding VistaGen, Dr. Snodgrass served as a key member of the executive management team that led Progenitor, Inc., a biotechnology company focused on developmental biology, through its initial public offering, and was its Chief Scientific Officer from June 1994 to May 1998, and its Executive Director from July 1993 to May 1994. He received his Ph.D. in immunology from the University of Pennsylvania, and has 23 years of experience in senior biotechnology management and over 10 years research experience as an assistant professor at the Lineberger Comprehensive Cancer Center, University of North Carolina Chapel Hill School of Medicine, and as a member of the Institute for Immunology, Basel, Switzerland. Dr. Snodgrass is a past Board Member of the Emerging Company Section of the Biotechnology Industry Organization (BIO), and past member of the International Society Stem Cell Research Industry Committee. Dr. Snodgrass has published more than 50 scientific papers, is the inventor on more than 17 patents and a number of patent applications, is, or has been, the Principal Investigator on U.S. federal and private foundation sponsored research grants with budgets totaling more than $14.5 million and is recognized as an expert in stem cell biology with more than 31 years' experience in the uses of stem cells as biological tools for research, drug discovery and development.

We selected Dr. Snodgrass to serve on our Board of Directors due to his expertise in biotechnology focused on developmental biology, including stem cell biology, his extensive senior management experience leading biotechnology companies at all stages of development, as well as his reputation and standing in the fields of biotechnology and stem cell research, allow him to bring to us and the Board of Directors a unique understanding of the challenges and opportunities associated with pluripotent stem cell biology, as well as credibility in the markets in which we operate.

Jerrold D. Dotson, CPA has served as our Chief Financial Officer since September 2011, as our Corporate Secretary since October 2013 and as a Vice President since February 2014. Mr. Dotson served as Corporate Controller for Discovery Foods Company, a privately held Asian frozen foods company from January 2009 to September 2011. From February 2007 through September 2008, Mr. Dotson served as Vice President, Finance and Administration (principal financial and accounting officer) for Calypte Biomedical Corporation (OTCBB: CBMC), a publicly held biotechnology company. Mr. Dotson served as Calypte's Corporate Secretary from 2001 through September 2008. He also served as Calypte's Director of Finance from January 2000 through July 2005 and was a financial consultant to Calypte from August 2005 through January 2007. Prior to joining Calypte, from 1988 through 1999, Mr. Dotson worked in various financial management positions, including Chief Financial Officer, for California & Hawaiian Sugar Company, a privately held company. Mr. Dotson is licensed as a CPA in California and received his B.S. degree in Business Administration with a concentration in accounting from Abilene Christian College.

Directors

Jon S. Saxe, J.D., LL.M. has served as Chairman of our Board of Directors since 2000. He also serves as the Chairman of our Audit Committee. Mr. Saxe is the retired President and was a director of PDL BioPharma from 1989 to 2008. From 1989 to 1993, he was President, Chief Executive Officer and a director of Synergen, Inc. (acquired by Amgen). Mr. Saxe served as Vice President, Licensing & Corporate Development for Hoffmann-Roche from 1984 through 1989, and Head of Patent Law for Hoffmann-Roche from 1978 through 1989. Mr. Saxe currently is a director of SciClone Pharmaceuticals, Inc. (NASDAQ: SCLN) and Durect Corporation (NASDAQ: DRRX), and six private life science companies, Arbor Vita Corporation, Arcuo Medical, LLC, Armetheon, Inc., Cancer Prevention Pharmaceuticals, Inc., Lumos Pharma, Inc. and Trellis Bioscience, Inc. Mr. Saxe also has served as a director of other biotechnology and pharmaceutical companies, including ID Biomedical (acquired by GlaxoSmithKline), Sciele Pharmaceuticals, Inc. (acquired by Shionogi), Amalyte (acquired by Kemin Industries), Cell Pathways (acquired by OSI Pharmaceuticals), and other companies, both public and private. Mr. Saxe has a B.S.Ch.E. from Carnegie-Mellon University, a J.D. degree from George Washington University and an LL.M. degree from New York University.

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We selected Mr. Saxe to serve as Chairman of our Board of Directors due to his numerous years of experience as a senior executive with major biopharmaceutical and biotechnology companies, including Protein Design Labs, Inc., Synergen, Inc. and Hoffmann-Roche, Inc., as well as his extensive experience serving as a director of numerous private and public biotechnology and pharmaceutical companies, serving as Chairman, and Chair and member of audit, compensation and governance committees of both private and public companies. Mr. Saxe provides us and our Board of Directors with highly valuable insight and perspective into the biotechnology and pharmaceutical industries, as well as the strategic opportunities and challenges that we face.

Brian J. Underdown, Ph.D. has served as a member of our Board of Directors since November 2009. Dr. Underdown is currently a Venture Partner with Lumira Capital Corp. having served as a Managing Director with Lumira from September 1997-December 2015. His investment focus has been on therapeutics in both new and established companies in both Canada and the United States. Prior to joining Lumira and its antecedent company MDS Capital Corp, Dr. Underdown held a number of senior management positions in the biopharmaceutical industry and at universities. Dr. Underdown's current board positions include the following private companies: enGene Inc. Formation Biologics and Osteo QC. Some of Dr. Underdown's previous board roles include: Argos Therapeutics (ARGS-Q), ID Biomedical (acquired by GSK), Ception Therapeutics (acquired by Cephalon). He has served on a number of Boards and advisory bodies of government-sponsored research organizations including CANVAC, the Canadian National Centre of Excellence in Vaccines, Ontario Genomics Institute (Chair), Allergen, the Canadian National Centre of Excellence in Allergy and Asthma. Dr. Underdown obtained his Ph.D. in immunology from McGill University and undertook post-doctoral studies at Washington University School of Medicine.

We selected Dr. Underdown to serve on our Board of Directors due to his extensive background working in the biotechnology and pharmaceutical industries, as a director of numerous private and public companies, as well as his venture capital experience funding and advising start-up and established companies focused on therapeutics.

Jerry B. Gin, Ph.D, M.B.A was appointed to serve on our Board of Directors on March 29, 2016. Dr. Gin is currently the co-founder and CEO of Nuvora, Inc., a private company founded in 2006 with a drug delivery platform for the sustained release of ingredients through the mouth for such indications as dry mouth, biofilm reduction and sore throat/cough relief. Dr. Gin is also co-founder and Chairman of Livionex, a private platform technology company founded in 2009 and focused on oral care, ophthalmology and wound care. Previously, Dr. Gin co-founded Oculex Pharmaceuticals in 1993, which developed technology for controlled release delivery of drugs to the interior of the eye, specifically to treat macular edema, and served as President and CEO until it was acquired by Allergan in 2003. Prior to forming Oculex, Dr. Gin co-founded and took public ChemTrak, which developed a home cholesterol test commonly available in drug stores today. Prior to ChemTrak, Dr. Gin was Director of New Business Development and Strategic Planning for Syva, the diagnostic arm of Syntex Pharmaceuticals, Director for Pharmaceutical and Diagnostic businesses for Dow Chemical, and Director of BioScience Labs (now Quest Laboratories), the clinical laboratories of Dow Chemical. Dr. Gin received his Bachelor's degree in Chemistry from the University of Arizona, his Ph.D. in Biochemistry from the University of California, Berkeley, his M.B.A. from Loyola College, and conducted his post-doctoral research at the National Institutes of Health.

We selected Dr. Gin to serve on our Board of Directors due to his extensive experience in the healthcare industry, focusing on founding and developing pharmaceutical, diagnostic and biotechnology companies and his expertise in propelling healthcare companies to their next platforms of growth.

Election of Executive Officers

Our executive officers are elected by, and serve at the discretion of, our Board of Directors. Each of our executive officers devotes his full time to our affairs. There are no family relationships among any of our directors or executive officers.

Board Composition

Our amended and restated bylaws provide that the authorized number of directors of the Company shall be not less than one nor more than seven, with the exact number of directors currently fixed at seven. The exact number may be amended only by the vote or written consent of a majority of the outstanding shares of our voting stock. Our Board of Directors currently consists of five members. Accordingly, there are currently two vacancies on our Board of Directors. Our Board of Directors anticipates filling each of such vacancies as soon as practicable. All actions of the Board of Directors require the approval of a majority of the directors in attendance at a meeting at which a quorum is present.

Board Committees

Our Board of Directors has established an Audit Committee, a Compensation Committee and a Corporate Governance and Nominating Committee. The composition and responsibilities of each committee are described below. Members serve on these committees until their resignation or until otherwise determined by our Board of Directors. Our independent directors, Mr. Saxe, Dr. Underdown and Dr. Gin, are each members of the Audit Committee. Mr. Saxe and Dr. Underdown also currently serve as members of the Compensation Committee and the Corporate Governance and Nominating Committee.

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Audit Committee

Our Audit Committee is comprised of Mr. Saxe, Dr. Underdown and Dr. Gin. Mr. Saxe is the chairman of our Audit Committee and is our Audit Committee financial expert, as that term is defined under SEC rules implementing Section 407 of the Sarbanes Oxley Act of 2002, and possesses the requisite financial sophistication, as defined under applicable rules. The Audit Committee operates under a written charter. Our Audit Committee charter is available on our website. Under its charter, our Audit Committee is primarily responsible for, among other things:

overseeing our accounting and financial reporting process;

selecting, retaining and replacing our independent auditors and evaluating their qualifications, independence and performance;

reviewing and approving scope of the annual audit and audit fees;

monitoring rotation of partners of independent auditors on engagement team as required by law;

discussing with management and independent auditors the results of annual audit and review of quarterly financial statements;

reviewing adequacy and effectiveness of internal control policies and procedures;

approving retention of independent auditors to perform any proposed permissible non-audit services;

overseeing internal audit functions and annually reviewing audit committee charter and committee performance; and

preparing the audit committee report that the SEC requires in our annual proxy statement.

Compensation Committee

Our Compensation Committee is comprised of Mr. Saxe and Dr. Underdown, who serve as the committee chairman. Our Compensation Committee charter is available on our website. Under its charter, the Compensation Committee is primarily responsible for, among other things:

reviewing and approving our compensation programs and arrangements applicable to our executive officers (as defined in Rule I 6a-I (f) of the Exchange Act), including all employment-related agreements or arrangements under which compensatory benefits are awarded or paid to, or earned or received by, our executive officers, including, without limitation, employment, severance, change of control and similar agreements or arrangements;

determining the objectives of our executive officer compensation programs;

ensuring corporate performance measures and goals regarding executive officer compensation are set and determining the extent to which they are achieved and any related compensation earned;

establishing goals and objectives relevant to CEO compensation, evaluating CEO performance in light of such goals and objectives, and determining CEO compensation based on the evaluation;

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endeavoring to ensure that our executive compensation programs are effective in attracting and retaining key employees and reinforcing business strategies and objectives for enhancing stockholder value, monitoring the administration of incentive-compensation plans and equity-based incentive plans as in effect and as adopted from time to time by the board;

reviewing and approving any new equity compensation plan or any material change to an existing plan; and

reviewing and approving any stock option award or any other type of award as may be required for complying with any tax, securities, or other regulatory requirement, or otherwise determined to be appropriate or desirable by the committee or board.

Corporate Governance and Nominating Committee

Our Corporate Governance and Nominating Committee is comprised of Mr. Saxe and Dr. Underdown, who serves as the committee chairman. Our Corporate Governance and Nominating Committee charter is available on our website. Under its charter, the Corporate Governance and Nominating Committee is primarily responsible for, among other things:

monitoring the size and composition of the board;

making recommendations to the board with respect to the nominations or elections of our directors;

reviewing the adequacy of our corporate governance policies and procedures and our Code of Business Conduct and Ethics, and recommending any proposed changes to the board for approval; and

considering any requests for waivers from our Code of Business Conduct and Ethics and ensure that we disclose such waivers as may be required by the exchange on which we are listed, if any, and rules and regulations of the SEC.

Code of Business Conduct and Ethics

We have adopted a Code of Business Conduct and Ethics applicable to our employees, officers and directors. Our Code of Business Conduct and Ethics is available on our website at www.vistagen.com. We intend to disclose any future amendments to certain provisions of our Code of Business Conduct and Ethics, or waivers of these provisions, on our website or in filings with the SEC under the Exchange Act.

Board Attendance at Board of Directors, Committee and Stockholder Meetings

Our Board of Directors met one time and acted by unanimous written consent eight times during the fiscal year ended March 31, 2016. Our Audit Committee met four times and our Compensation Committee requested action by the entire Board of Directors for grants of warrants and the modification of certain warrants during the same period. Our Nominating and Corporate Governance Committee requested action by the entire Board of Directors with respect to the March 2016 appointment of Dr. Gin to the Board and Audit Committee. Each director serving during fiscal 2016 attended all of the meetings of the Board and the committees of the Board upon which such director served that were held during the term of his service.

We do not have a formal policy regarding attendance by members of the Board at our annual meeting of stockholders, but directors are encouraged to attend. We did not hold an annual meeting of stockholders during our fiscal year ended March 31, 2016.

Compensation Committee Interlocks and Insider Participation

Our Compensation Committee consists of Dr. Underdown and Mr. Saxe, each of whom is a non-employee director. Neither member of the Compensation Committee has a relationship that would constitute an interlocking relationship with executive officers or directors of another entity.

Section 16 Beneficial Ownership Reporting Compliance

Section 16(a) of the Exchange Act requires our officers, directors and persons who beneficially own more than ten percent of our common stock (collectively, Reporting Persons) to file reports of ownership on Form 3 and changes in ownership on Form 4 or Form 5 with the SEC. The Reporting Persons are also required by SEC rules to furnish us with copies of all reports that they file pursuant to Section 16(a). We believe that during our fiscal year ended March 31, 2016, all of the Reporting Persons, other than Platinum Long Term Growth VII and/or its affiliate, Montsant Partners LLC, Michael Goldberg, Cato BioVentures, and Morrison & Foerster LLP, complied with all applicable reporting requirements.

EXECUTIVE COMPENSATION

Our Compensation Objectives

Our compensation practices are designed to attract key employees and to retain, motivate and reward our executive officers for their performance and contribution to our long-term success. Our Board of Directors, through the compensation committee, seeks to compensate our executive officers by combining short and long-term cash and equity incentives. It also seeks to reward the achievement of corporate and individual performance objectives, and to align executive officers' incentives with stockholder value creation. When possible, the compensation committee seeks to tie individual goals to the area of the executive officer's primary responsibility. These goals may include the achievement of specific financial or business development goals. Also, when possible and appropriate taking into account the Company's financial condition and other related facts and circumstances, the compensation committee seeks to set performance goals that reach across all business areas and include achievements in finance/business development and corporate development.

The Compensation Committee makes decisions regarding salaries, annual bonuses, if any, and equity incentive compensation for our executive officers, approves corporate goals and objectives relevant to the compensation of the Chief Executive Officer and our other executive officers. The Compensation Committee solicits input from our Chief Executive Officer regarding the performance of our other executive officers. Finally, the Compensation Committee also administers our incentive compensation and benefit plans.

Although we have no formal policy for a specific allocation between current and long-term compensation, or cash and non-cash compensation, when possible and appropriate taking into account the Company's financial condition and other related facts and circumstances, we seek to implement a pay mix for our officers with a relatively equal balance of both, providing a competitive salary with a significant portion of compensation awarded on both corporate and personal performance.

Compensation Components

As a general rule, and when possible and appropriate taking into account the Company's financial condition and other related facts and circumstances, our compensation consists primarily of three elements: base salary, annual bonus and long-term equity incentives. We describe each element of compensation in more detail below.

Base Salary

Base salaries for our executive officers are established based on the scope of their responsibilities and their prior relevant experience, taking into account competitive market compensation paid by other companies in our industry for similar positions and the overall market demand for such executives at the time of hire. An executive officer's base salary is also determined by reviewing the executive officer's other compensation to ensure that the executive officer's total compensation is in line with our overall compensation philosophy.

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Base salaries are reviewed annually and increased for merit reasons, based on the executive officers' success in meeting or exceeding individual objectives. Additionally, we adjust base salaries as warranted throughout the year for promotions or other changes in the scope or breadth of an executive officer's role or responsibilities. As indicated in the following Summary Compensation Table, to conserve our cash resources during fiscal 2015 and fiscal 2014 the cash amounts of annual base salary that we paid to our executives was significantly less than their stated annual base salary rates.

Annual Bonus

The Compensation Committee assesses the level of the executive officer's achievement of meeting individual goals, as well as that executive officer's contribution towards our corporate-wide goals. The amount of the cash bonus depends on the level of achievement of the individual performance goals, with a target bonus generally set as a percentage of base salary and based on the achievement of pre-determined milestones. To conserve our cash resources, our management team voluntarily decided to not seek and, in accordance with our management team's election, our Compensation Committee did not award cash bonuses in any fiscal year from 2012 through 2015.

Long-Term Equity Incentives

The Compensation Committee believes that to attract and retain management, key employees and non-management directors the compensation paid to these persons should include, in addition to base salary and potential annual cash incentives, equity based compensation that is competitive with peer companies. The Compensation Committee determines the amount and terms of equity-based compensation granted under our stock option plans or pursuant to other awards made to our executives and key employees.

Summary Compensation Table

The following table shows information regarding the compensation of our Named Executive Officers (NEO's) for services performed in the fiscal years ended March 31, 2016 and 2015:

Name and Principal Position	Fiscal Year	Salary ($)	Bonus ($)	Option and Warrant Awards (7) ($)	All Other Compensation ($)	Total ($)
Shawn K. Singh (1) Chief Executive Officer	2016	347,500	-	1,629,574(8)	-	1,977,074