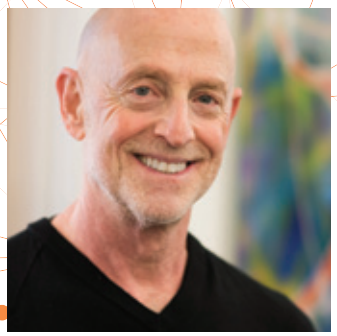
2016 ANNUAL REPORT

SAGE THERAPEUTICS



April 20, 2017

TO OUR SHAREHOLDERS

WE ARE PROUD OF THE PROGRESS WE HAVE MADE in almost three years since our initial public offering. Sage is continuing its vision to "rethink" the development of treatments for central nervous system (CNS) disorders and, in doing so, attempting to close the innovation gap in an area of disease that represents approximately one-third of the worldwide burden of illness. The human brain is a complex, integrated network, and this has provided a challenge in developing new treatments for CNS diseases. Conventional approaches have failed to provide breakthroughs in treating a number of brain disorders, and to this day new treatments are needed to address these unmet needs. Our primary focus at Sage is on delivering truly differentiated medicines developed through innovative approaches to research and development, with a corporate dedication to making people's lives better. In 2017, we have achieved significant momentum following progress across our pipeline in 2016. We expect to report results from a number of clinical trials this year, including our Phase 3 clinical programs, which, if positive, will put us on the cusp of a potential product commercialization in 2018.

Sage is advancing a portfolio of novel CNS product candidates targeting the GABA and NMDA receptor systems. Dysfunction in these systems is known to be at the core of numerous psychiatric and neurological disorders. We believe that Sage is pursuing a unique, data-driven approach to CNS drug development by employing efficient human proof-of-concept studies not only to uncover both activity signals, but also to guide the design of future clinical trials before investing in larger programs.

We are developing our lead product candidate, brexanolone (SAGE-547) in two separate Phase 3 clinical programs – one program studying brexanolone as an acute interventional treatment for super-refractory status epilepticus (SRSE), and a second program for the treatment of postpartum depression (PPD). Brexanolone is Sage's proprietary IV formulation of allopregnanolone, a naturally occurring neuroactive steroid that acts as a synaptic and extrasynaptic modulator of the $GABA_A$ receptor.

Our Phase 3 STATUS Trial is a global, randomized, double-blind, placebo-controlled trial, designed to evaluate brexanolone as a potential adjunctive therapy for SRSE, a rare and life-threatening seizure condition. The Phase 3 clinical program is being conducted with a design that is based on an agreement with the U.S. Food and Drug Administration (FDA) under a Special Protocol Assessment (SPA). In the fourth quarter of 2016, Sage also received positive scientific advice on the development of brexanolone in SRSE from the European Medicines Agency (EMA). Based on this advice, we believe the Phase 3 clinical program, if successful, will be sufficient to support submission of a marketing authorization application (MAA) to the EMA seeking approval of brexanolone for SRSE in the EU.

Sage is also conducting a Phase 3 clinical program evaluating brexanolone as a potential treatment for PPD, a distinct and readily identified major depressive disorder that is a biological complication of childbirth. This program consists of two studies – a placebo-controlled trial in severe PPD patients and another in moderate PPD patients, collectively known as the Hummingbird Study. In 2016, the FDA granted Breakthrough Therapy Designation and the EMA granted PRIority MEdicines (PRIME) designation to brexanolone for the treatment of PPD.

Sage's most advanced, next-generation product candidate is SAGE-217, a novel, orally-active neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. In the fourth quarter of 2016, Sage initiated Phase 2 development for SAGE-217 in various mood and movement disorders, with four Phase 2 clinical programs now underway in major depressive disorder, PPD, essential tremor and Parkinson's disease.

Sage is also currently evaluating a series of novel GABA modulators in pre-clinical development, including SAGE-324 and SAGE-689. Sage has initiated IND-enabling studies of SAGE-324, a novel, orally-active next-generation modulator intended to be developed for GABA-related indications such as orphan epilepsies and other disorders involving GABA hypofunction.

We are also developing novel compounds that target the NMDA receptor, a critical excitatory receptor system implicated in a broad range of CNS disorders and an area of research that we are seeking to help pioneer. SAGE-718, a unique, first-in-class oral compound, has completed IND-enabling studies, and Sage expects to initiate Phase 1 clinical development for SAGE-718 in the first half of 2017.

On the corporate side, we continued to grow our team in order to position Sage for long-term success. We have expanded with over 160 employees, including key development, research, technical operations and medical affairs appointments. We also continue to make important progress in expanding our commercial team to prepare for potential near-term commercialization, including hires in market access, payor management and sales and marketing.

In 2017, our key objectives include:

- Completing Phase 3 clinical development of brexanolone in both SRSE and PPD, and, if successful, expeditiously filing for regulatory approval;
- Preparing for a potential commercial launch of brexanolone in both SRSE and PPD;
- Advancing Phase 2 development of our next generation oral compound, SAGE-217, in mood and movement disorders;
- Advancing our lead NMDA modulator, SAGE-718, into Phase 1 clinical development;
- Continuing discovery and development of other novel compounds, including IND-enabling studies for SAGE-324;
- And further growing our translational science expertise to better enhance the probability of future development success.

We are extremely proud of the great work and progress achieved by the Sage team towards our goal of delivering therapies that we hope will advance science in the service of making people's lives better. As always, we thank our clinical collaborators, board members and stockholders for their continued support. Most importantly, we want to thank the people who have participated in our clinical trials. Without their support and commitment, we would not be able to pursue our goal of developing truly novel, differentiated medicines that can make a difference in people's lives. While we are proud of our progress over the past three years, we are even more excited by what lies ahead.

Sincerely,

Jeff Jonas, M.D.
Chief Executive Officer

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

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2016

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from _____ to _____

Commission file number: 001-36544

Sage Therapeutics, Inc.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**27-4486580**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**
215 First Street Cambridge, Massachusetts	**02142**
(Address of Principal Executive Offices)	**(Zip Code)**

(617) 299-8380
(Registrant's Telephone Number, Including Area Code)

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.0001 par value	**NASDAQ Global Market**

Securities registered pursuant to Section 12(g) of the Act: None

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

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

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

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

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

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

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

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

The aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) as of June 30, 2016 was approximately $670,259,868, computed by reference to the closing price of the registrant's common stock on the NASDAQ Global Market reported for such date.

As of February 15, 2017, there were 37,270,180 shares of common stock, $0.0001 par value per share, outstanding.

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Cautionary Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "may", "will", "should", "expects", "intends", "plans", "anticipates", "believes", "estimates", "predicts", "potential", "continue" or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- our plans to develop and commercialize our product candidates in the central nervous system, or CNS, disorders we discuss in this Annual Report, and potentially in other indications;
- our ability, within the expected timeframes, to complete our ongoing non-clinical studies and clinical trials; to announce the results of such studies and trials; to advance our product candidates into additional clinical trials, including pivotal clinical trials; and to successfully complete such clinical trials;
- our expectations as to the sufficiency of the planned clinical development programs for our product candidates, if successful, to support regulatory approval; our plans with respect to filing for regulatory approval of our product candidates, if clinical development is successful; and the anticipated review path and potential to obtain regulatory approval and to commercialize any product, if approved;
- our estimates regarding expenses; use of cash; timing of future cash needs; and capital requirements;
- the potential for future revenues;
- our expectations with respect to the availability of supplies of our product candidates, and the expected performance of our third-party manufacturers;
- our expectations with respect to the performance of our contract research organizations and other third parties whose activities are important to our development and future commercialization efforts;
- our ability to obtain and maintain intellectual property protection for our proprietary assets and other forms of exclusivity relevant to our business;
- the estimated number of patients in indications of interest to us; the potential for our product candidates in those indications, if approved; the size of the potential markets for our product candidates; and our ability to serve those markets;
- the anticipated rate and degree of market acceptance of our product candidates for any indication if approved;
- our plans for expanding our activities, including outside the U.S., and the potential for future collaborations and other types of contractual relationships, if appropriate, for accomplishing our strategic objectives;
- the level of costs we may incur in connection with our activities, the possible timing and sources of future financings, and our ability to obtain additional financing when needed;
- the potential for success of competing products that are or become available for the indications that we are pursuing or may in the future pursue;
- the potential risk of loss of key scientific or management personnel; and
- other risks and uncertainties, including those listed under Part II, Item 1A, Risk Factors.

Any forward-looking statements in this Annual Report reflect our current views with respect to future events and with respect to our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those described under Part II, Item 1A, Risk Factors and elsewhere in this Annual Report. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report contains estimates, projections and other information concerning our industry, the general business environment, and the markets for certain diseases, including estimates regarding the potential size of those markets and the estimated incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties, and actual events, circumstances or numbers, including actual disease prevalence rates and market size, may differ materially from the information reflected in this Annual Report. Unless otherwise expressly stated, we obtained this industry, business information, market data, prevalence information and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data, and similar sources, in some cases applying our own assumptions and analysis that may, in the future, prove not to have been accurate.

PART I

All brand names or trademarks appearing in this report are the property of their respective owners. Unless the context requires otherwise, references in this report to "Sage" the "Company," "we," "us," and "our" refer to Sage Therapeutics, Inc. and its subsidiaries.

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat life-altering central nervous system, or CNS, disorders, where there are no approved therapies or existing therapies are inadequate. We have a portfolio of product candidates with a current focus on modulating two critical CNS receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of $GABA_A$ receptors. The NMDA-type receptors of the glutamate receptor system are a major excitatory receptor system in the CNS. Dysfunction in these systems is implicated in a broad range of CNS disorders. We are targeting CNS indications where patient populations are easily identified, clinical endpoints are well-defined, and development pathways are feasible.

Our lead product candidate, SAGE-547 (brexanolone USAN), is a proprietary intravenous, or IV, formulation of allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors, including both synaptic and extrasynaptic populations. We are currently conducting Phase 3 clinical trials of SAGE-547 in both super-refractory status epilepticus, or SRSE, and post-partum depression, or PPD.

Our Phase 3 clinical trial in SRSE, known as the STATUS Trial, is evaluating SAGE-547 as a potential adjunctive therapy in the treatment of SRSE. SRSE is a rare and life-altering condition in which a patient experiences a state of continuous seizure called status epilepticus, or SE, that continues or recurs despite standard treatment regimens normally sufficient to stop the seizure activity. We expect to report top-line results from the STATUS Trial in the first half of 2017. If successful, we believe the results from this Phase 3 clinical trial, together with other data from the SAGE-547 development program will be sufficient to form the basis of a New Drug Application, or NDA, submission to the FDA seeking approval for SAGE-547 in SRSE in the U.S. Based on scientific advice we received in the fourth quarter of 2016 from the European Medicines Agency, or EMA, we also believe our current Phase 3 clinical program in SRSE, if successful, will be sufficient to support a marketing authorization application, or MAA, to the EMA seeking approval of SAGE-547 for SRSE in the European Union, or EU.

Our Phase 3 clinical program in PPD is evaluating SAGE-547 as a potential treatment for PPD. PPD is a distinct and readily identified major depressive disorder that is a biological complication of childbirth, affecting a subset of women typically commencing in the third trimester of pregnancy or within four weeks after giving birth. We anticipate announcing top-line data from the Phase 3 clinical program, known as the Hummingbird Study, encompassing two placebo-controlled trials, in the second half of 2017. In the third quarter of 2016, we received Breakthrough Therapy designation from the FDA for SAGE-547 as a potential treatment for PPD. Based on input we received from the FDA during a Breakthrough Therapy meeting in the fourth quarter of 2016, we believe that, if successful, the results of the Phase 3 clinical program, together with the results of prior clinical studies of SAGE-547 in PPD, and ongoing non-clinical studies, will be sufficient to support the submission of an NDA to the FDA seeking approval for SAGE-547 in PPD. In the fourth quarter of 2016, we also received **PRI**ority **ME**dicines (PRIME) designation from the EMA for SAGE-547 in the treatment of PPD.

Our most advanced next-generation product candidate is SAGE-217, a novel neuroactive steroid that, like SAGE-547, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. In the fourth quarter of 2016, we initiated our Phase 2 clinical program for SAGE-217 with a focus on four indications: two movement disorder indications, essential tremor and Parkinson's disease, and two mood disorder indications, major depressive disorder, or MDD, and PPD. In February 2017, we announced top-line results from the open-label, proof-of-concept portion (Part A) of our Phase 2 clinical trial of SAGE-217 in MDD which met our criteria for advancing SAGE-217 into the blinded, placebo-controlled portion of the Phase 2 MDD clinical trial (Part B). We expect to initiate Part B in the second quarter of 2017. We are also currently conducting the Phase 2 clinical trials of SAGE-217 in PPD, essential tremor and Parkinson's disease. We expect to report top-line results from the open-label portion of the Phase 2 clinical trial of SAGE-217 in Parkinson's disease in the first half of 2017. We anticipate reporting top-line results from the blinded, placebo-controlled Phase 2 clinical trials of SAGE-217 in essential tremor and PPD in the second half of 2017. We also have a portfolio of other novel compounds that target the $GABA_A$ receptors, including SAGE-105, SAGE-324 and SAGE-689, which are at earlier stages of development with a focus on both acute and chronic CNS disorders.

Our second area of focus is the development of novel compounds that target the NMDA receptor. The first product candidate selected for development from this program is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor. Our initial areas of focus for development of SAGE-718 will be cerebrosterol deficit disorders, Anti-NMDA Receptor Encephalitis, and other indications involving NMDA receptor hypofunction. We believe measuring levels of anti-NMDA receptor antibodies or decreased levels of cerebrosterol, a naturally occurring oxysterol, may represent biomarkers to identify, for future study, broader patient populations characterized by cognitive dysfunction and neuropsychiatric symptoms resulting from NMDA receptor dysfunction or hypofunction. Examples of these potential areas for future evaluation include certain types, aspects or subpopulations of a number of diseases such as depression, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, Huntington's disease, and neuropathic pain. We have completed Investigational New Drug, or IND-enabling non-clinical studies of SAGE-718, and plan to commence the Phase 1 clinical program in the first half of 2017.

We expect to continue our focus on allosteric modulation of the $GABA_A$ and NMDA receptor systems in the brain. The $GABA_A$ and NMDA receptor systems are broadly accepted as impacting many psychiatric and neurological disorders, spanning disorders of mood, seizure, cognition, anxiety, sleep, pain, epilepsy, and movement disorders, among others. We believe that we will have the opportunity to develop molecules from our internal portfolio with the goal of addressing a number of these disorders in the future. Our ability to identify and develop such novel CNS therapies is enabled by our proprietary chemistry platform that is centered, as a starting point, on knowledge of the chemical scaffolds of certain endogenous neuroactive steroids. We believe our knowledge of the chemistry and activity of allosteric modulators allows us to efficiently design molecules with different characteristics. This diversity enables us to regulate important properties such as half-life, brain penetration and receptor pharmacology to develop product candidates that have the potential for better selectivity, increased tolerability, and fewer off-target side effects than either current CNS therapies or previous therapies which have failed in development.

Our Strategy

Our goal is to continue to be a leading biopharmaceutical company focused on development and commercialization of novel proprietary therapies for the treatment of life-altering CNS disorders. Key elements of our strategy are to:

- Complete Phase 3 clinical development of SAGE-547 as a treatment for both SRSE and PPD, and, if successful, expeditiously file for regulatory approval.
- Prepare for a potential commercial launch of SAGE-547 in both SRSE and PPD, and build commercial capability to bring SAGE-547 and other CNS therapeutics, if and when approved, to physicians and patients for the approved indications.
- Rapidly advance development of our next generation product candidate, SAGE-217, in movement and mood disorders, to determine which indications, if any, are appropriate to continue further in development.
- Continue development of other novel compounds that act through allosteric modulation of the $GABA_A$ receptor such as SAGE-105 and SAGE-324.
- Advance SAGE-718 into clinical development, and diversify our efforts by also focusing on other novel compounds that target the NMDA receptor.
- Grow our product candidate pipeline more broadly utilizing the strengths of our proprietary chemistry platform and translational science expertise, and focusing our development activities on CNS indications where we can make well-informed, rapid go/no-go decisions to facilitate long-term growth.
- Enhance the probability of future success by utilizing our discovery research expertise to continue to design unique compounds with differentiated features, with a continued focus on allosteric modulation of the $GABA_A$ and NMDA receptor systems in the brain.
- Continue to refine and execute possible strategic options for development and potential future commercialization of product candidates outside the U.S. and Canada.

Understanding the Foundations of Our Approach

Neurotransmission

The CNS is composed of a vast and complex network of different structures and cell types, most of which serve directly or indirectly, to provide a means for the nervous system to signal or communicate with other nerve cells in order to regulate and control all brain function. The cell type responsible for this signaling is called a neuron. One way chemical or electrical signals exert their effects on neurons is by traveling across a physical gap located between two neurons, called a synapse. Presynaptic neurons transmit signals whereas postsynaptic neurons react to the signals. The human brain contains approximately 86 billion neurons, each having

hundreds to tens of thousands of synapses to allow for this communication. This process is essential to all things, from organ function, to movement, to memory and all behavioral processes.

Neurotransmission is the process by which signaling molecules, called neurotransmitters, are released by a presynaptic neuron, travel over the synaptic space and bind to and interact with receptors on a postsynaptic neuron. Depending on the nature of the neurotransmitter and receptor, this interaction results in excitation, inhibition or modulation of the receiving neuron's behavior.

Synaptic receptors are primarily located inside the synaptic cleft, or the space where the neurons communicate, and have been historically considered to be the most important part of the neuron. However, recent understanding of neurotransmission and brain function has shown there are many extrasynaptic receptors that also respond to neurotransmitters to exert their effects. For example, it is becoming increasingly understood that extrasynaptic $GABA_A$ receptor-mediated neurotransmission is critical to generalized neurological function and has demonstrated influence over general physiological states such as sleep, hunger, anxiety and seizure, among other things.

Allosteric Modulation

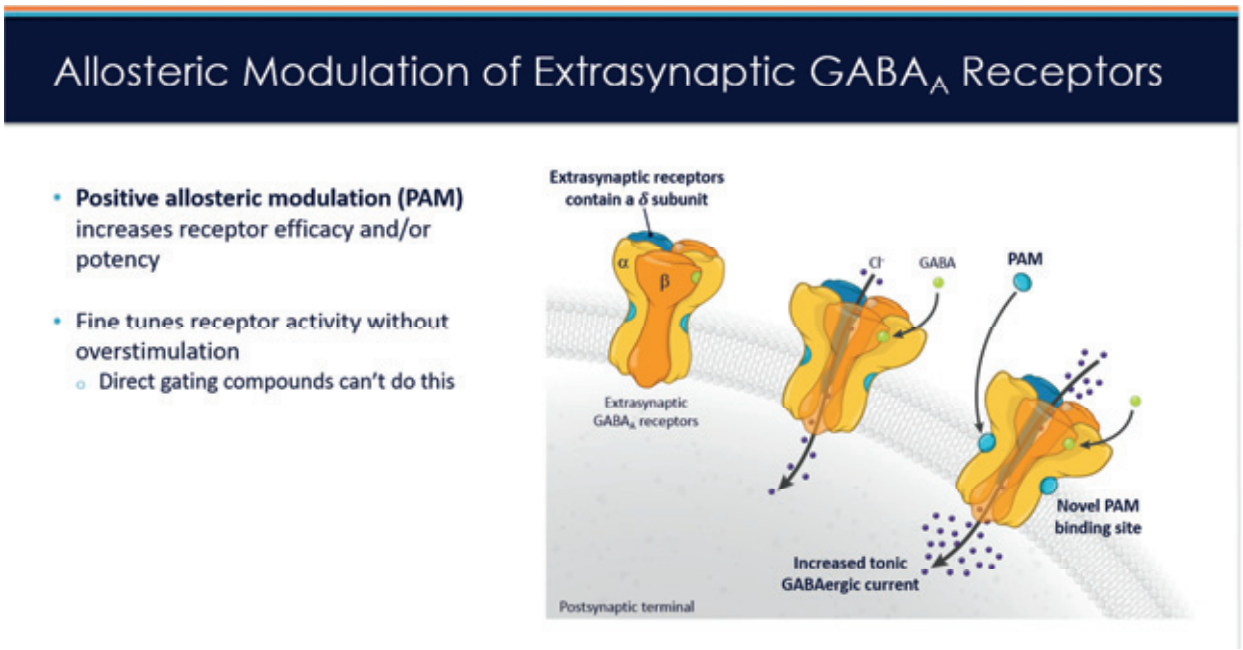
We are focused on developing drugs based on selective allosteric modulation of key CNS synaptic and extrasynaptic receptors. Molecules that function directly on synaptic or extrasynaptic receptors at the site where the native, or natural, molecule binds to inhibit or activate them are known as orthosteric molecules. Alternatively, allosteric modulators are a class of small molecules very different from classical orthosteric drugs, as allosteric modulators interact at a site different from the native site and allow the potential for fine-tuning of neuronal signals.

Orthosteric drugs aimed at key synaptic receptors typically have a targeted effect of complete activation or complete inhibition of the neuron, with little subtlety in how they exert their effect. As a result, neurons may be unable to respond to normal stimuli, and can become over-stimulated by a neurotransmitter or be unable to respond to normal neurotransmission, thus potentially negatively impacting both the efficacy and safety profile of an orthosteric CNS drug development candidate. We believe that nowhere in the body is it more important to maintain normal rhythms than in the brain, and accordingly we believe that allosteric modulation approaches are well-suited for the treatment of CNS diseases and disorders.

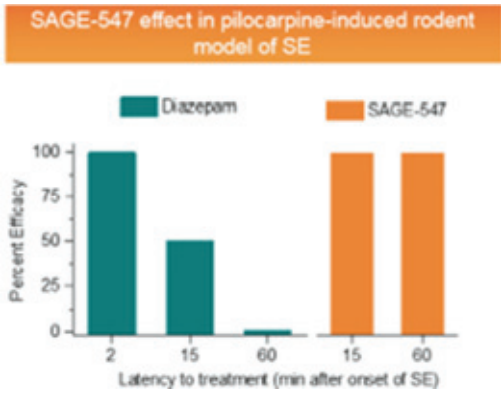
We utilize our proprietary chemistry capabilities to design and identify drugs that are allosteric modulators that bind to either or both synaptic and extrasynaptic receptors, and that have properties targeted to the indications of interest. Our goal is to select for development compounds that we believe are capable of varying degrees of desired activity rather than complete activation or inhibition of the receptor as is typically observed with orthosteric drugs. Our current focus is on developing compounds that are positive allosteric modulators of both synaptic and extrasynaptic sites of either the $GABA_A$ receptor or the NMDA receptor system.

Allosteric Modulation of Extrasynaptic $GABA_A$ Receptors

$GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the human brain, playing a key role in reducing neuron excitability. Our initial focus is on the development of positive allosteric modulators of both synaptic and extrasynaptic sites of the $GABA_A$ receptor. Benzodiazepines, or BDZs, are allosteric modulators that primarily act at a particular receptor, the synaptic $GABA_A$ receptor, with little or no activity at extrasynaptic sites. We believe we can enhance the potential utility of modulating the $GABA_A$ receptor for certain indications, and effectively avoid some of the limitations of BDZs, by developing compounds that bind to both synaptic and extrasynaptic $GABA_A$ receptors. The extrasynaptic $GABA_A$ receptor is structurally distinct from the synaptic receptor, possesses unique pharmacology and is located in a different place than the synaptic $GABA_A$ receptor. In addition, the extrasynaptic $GABA_A$ receptor remains intact during prolonged periods of seizure with no down-regulation while synaptic $GABA_A$ receptors are down-regulated, or diminished in their activity causing, for example, some refractory SE patients to be resistant to the action, or pharmacology, of drugs that only target the synaptic $GABA_A$ receptors, such as BDZs. Published non-clinical testing utilizing well-validated animal models of SE and sophisticated instruments for identifying the expression of both synaptic and extrasynaptic $GABA_A$ receptors on the surface of neurons support this hypothesis. These studies, performed in rats, showed a reduced number and activity of synaptic $GABA_A$ receptors during SE, in contrast to the preserved number and activity of extrasynaptic $GABA_A$ receptors under the same conditions. These studies were done by measuring the amount of $GABA_A$ synaptic and $GABA_A$ extrasynaptic receptors that are present on the surface of the neurons. The analysis of protein present for each of the respective receptors in animals in the SE-state, versus normal animals, shows the difference in $GABA_A$ receptor expression.



The figure below shows the results of a rodent study where the subject animals were placed into an SE-like condition of prolonged seizure resulting in continuous spontaneous seizures. SAGE-547 was then administered to certain animals while the others received a BDZ. In this animal model, BDZs were unable to adequately control the seizure condition which we believe is due to down-regulation of synaptic GABA$_A$ receptors. In contrast, SAGE-547, working at both synaptic and extrasynaptic GABA$_A$ receptors, appears to have treated the seizures in these animals and resolved their SE.

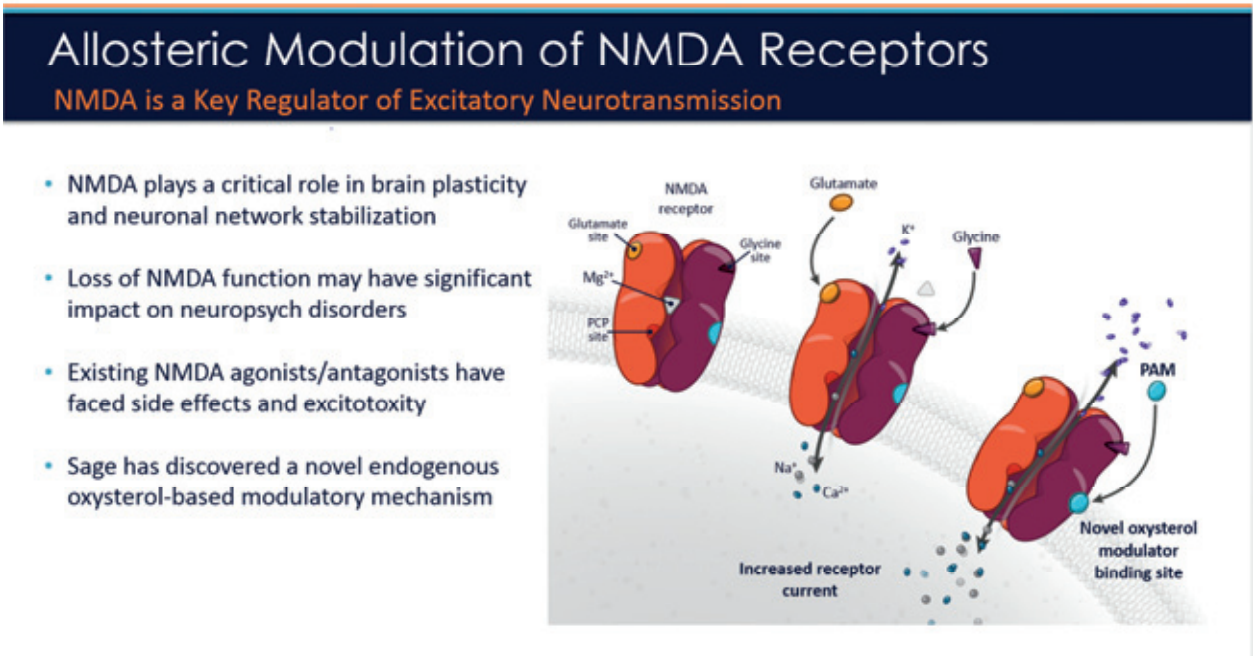


Allosteric Modulation of NMDA Receptors to Address Certain CNS Conditions

NMDA receptors serve a critical role in CNS-related activities. Orthosteric drug candidate approaches to modulating the NMDA receptor have also been fraught with difficulties. NMDA receptor antagonists have been explored for treating Alzheimer's disease and neuropathic pain and for inducing anesthesia. Drugs that antagonize NMDA receptors have generally been limited by adverse effects, such as neurotoxicity, deteriorating mental status and psychotomimetic, or the onset of psychotic symptoms, following the administration of the drug. NMDA receptor agonists have been tested in schizophrenia, and many believe that they may have a role in enhancing cognition and mood. However, their ability to be used at effective doses in humans has generally been limited by non-clinical findings indicating these agents may induce cell death through excess excitation of nerve cells.

We have identified, and continue to evaluate, a number of positive and negative allosteric modulators of the NMDA receptor that we believe have the potential to overcome the difficulties associated with orthosteric approaches. Like our GABA$_A$ allosteric modulators, our NMDA receptor allosteric modulators work at sites located in the synaptic and extrasynaptic spaces of the neuron and enhance, or modulate, the activity of the native molecule without directly activating the NMDA receptor. Initial animal testing of our NMDA receptor allosteric modulators has provided evidence that targeting the synaptic and extrasynaptic spaces may help avoid the

excitotoxicity and psychotomimesis observed with directly activating, orthosteric compounds. This in turn may eventually allow us to discover and develop, alone or with partners, compounds to treat certain conditions where NMDA receptor dysfunction may play a role in cognitive dysfunction and neuropsychiatric symptoms such as certain types, aspects or subpopulations of depression, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, Huntington's disease, and neuropathic pain.



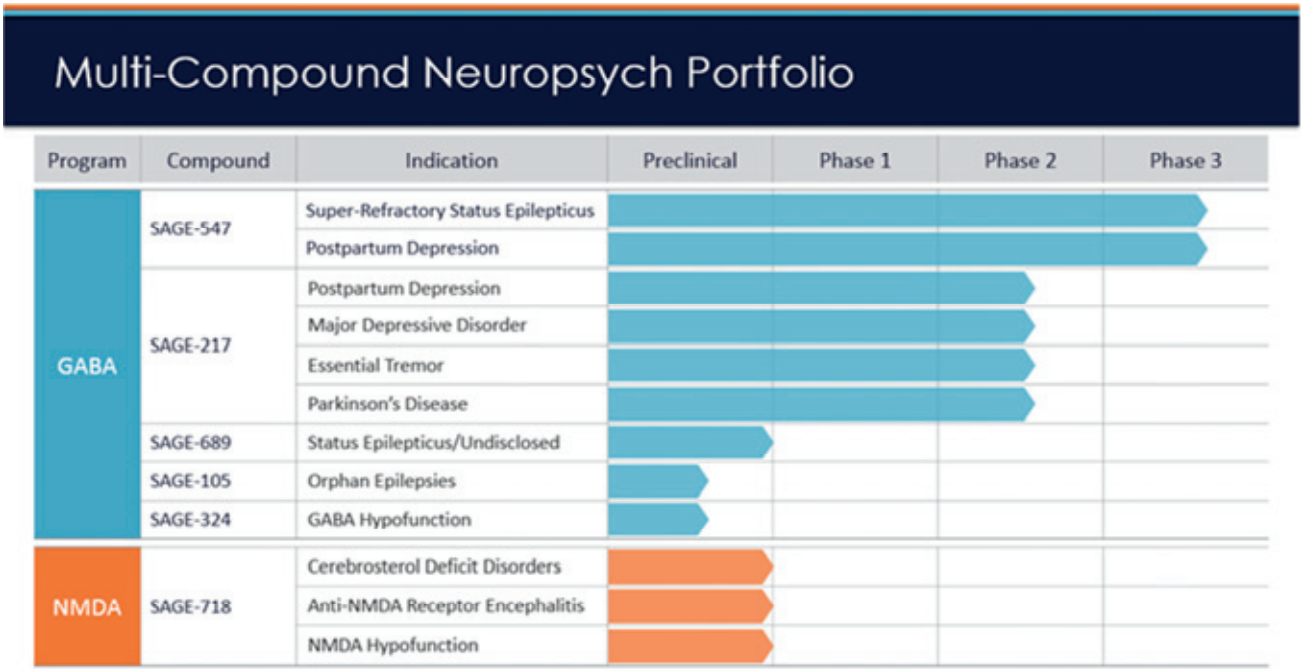
Our proprietary chemistry platform

Our proprietary chemistry platform is centered, as a starting point, on knowledge of the chemical scaffolds of endogenous neuroactive steroids that are allosteric modulators of $GABA_A$ or NMDA receptors. We have leveraged this platform to assemble a chemistry portfolio of greater than 2,000 compounds. We believe our proprietary chemistry platform allows us to:

- optimize the properties of neuroactive steroid compounds to develop proprietary, new chemical entities, with the potential to be used as oral, IV, or intramuscular therapies;
- control important properties such as half-life, brain penetration and the types of receptors our drugs act upon, thereby modulating either inhibition or excitation either acutely or chronically; and
- create drugs that are designed to exert control over the intensity of receptor activation or deactivation, with the potential to hit targets in the brain with more precision, with the goal of increased tolerability and fewer off-target side effects than current CNS therapies.

Our Product Pipeline

The following table summarizes the status of our development programs as of the date of this Annual Report:



SAGE-547

Overview

Our lead product candidate, SAGE-547, is in Phase 3 clinical development both as a potential adjunctive therapy in the treatment of SRSE and as a potential treatment for PPD. SAGE-547 is a proprietary IV formulation of synthesized allopregnanolone, a naturally occurring neurosteroid that acts as a synaptic and extrasynaptic modulator of the $GABA_A$ receptor.

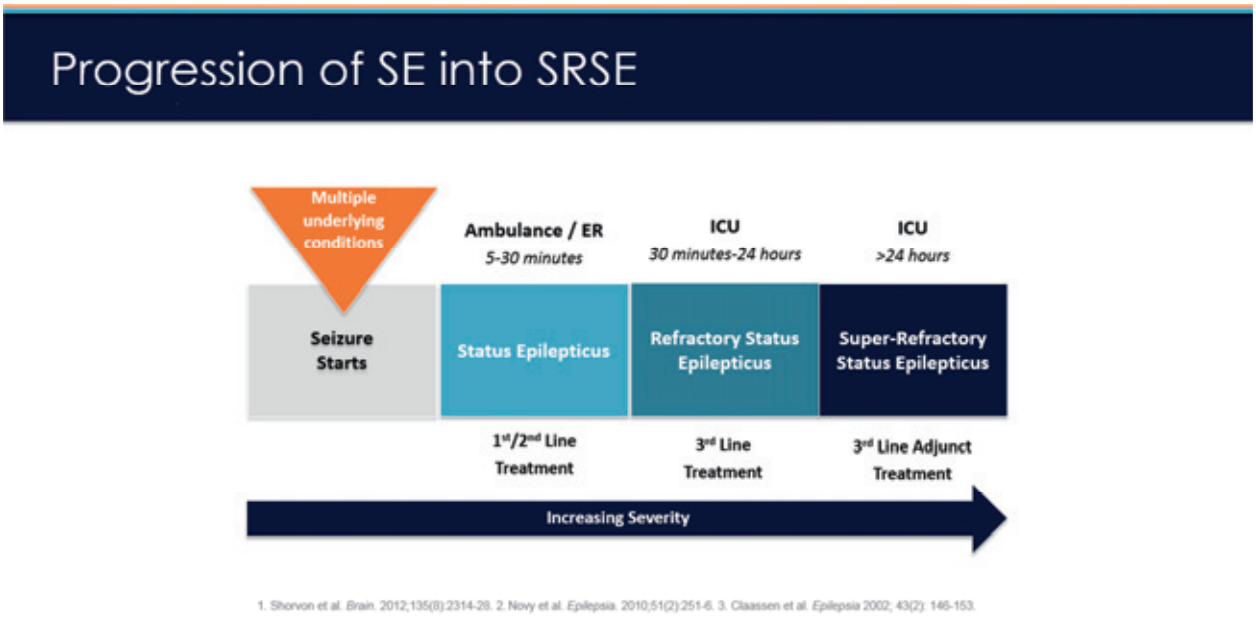
Our Phase 3 clinical trial of SAGE-547 in SRSE, known as the STATUS Trial (SAGE-547 Treatment as Adjunctive Therapy Utilized in Status Epilepticus), is a global, randomized, double-blind, placebo-controlled Phase 3 clinical trial to evaluate SAGE-547 as a treatment for patients with SRSE. Enrollment in the STATUS Trial is ongoing. We expect to announce top-line results from the STATUS Trial in the first half of 2017. If successful, we believe the results from this Phase 3 clinical trial, together with other data obtained from the SAGE-547 development program, will be sufficient to form the basis of an NDA submission for SAGE-547 in the U.S. in SRSE. The FDA has granted us orphan drug designation for SAGE-547 in the treatment of SE, including SRSE, and Fast Track designation for our IND for SAGE-547 as a treatment for SRSE. Based on scientific advice we received in the fourth quarter of 2016 from the EMA, we also believe our current Phase 3 clinical program in SRSE, if successful, will be sufficient to support an MAA filing with the EMA seeking approval of SAGE-547 for SRSE in the EU.

The Phase 3 clinical trials of SAGE-547 in PPD, known together as the Hummingbird Study, are comprised of a randomized, placebo-controlled dose-ranging clinical trial of SAGE-547 in patients with severe PPD and a randomized, placebo-controlled clinical trial to evaluate SAGE-547 efficacy and safety in patients with moderate PPD. We anticipate announcing top-line data from the Hummingbird Study in the second half of 2017. In the third quarter of 2016, we received Breakthrough Therapy Designation from the FDA for SAGE-547 as a potential treatment for PPD. Breakthrough Therapy Designation is intended to offer a potentially expedited development path and review for promising drug candidates, which includes increased interaction and guidance from the FDA. In December 2016, we announced input from an FDA Breakthrough Designation meeting confirming that our ongoing clinical trial in PPD, with minor modifications, including increased sample size, is considered a Phase 3 clinical trial. Based on input from the FDA, we believe that, if successful, the results of the Hummingbird Study, together with the results of prior clinical studies of SAGE-547 in PPD, and ongoing non-clinical studies, will be sufficient to support the submission of an NDA with the FDA for SAGE-547 in the treatment of PPD. In the fourth quarter of 2016, we also received PRIME designation from the EMA for SAGE-547 in the treatment of PPD. The PRIME program was launched by the EMA in March 2016, and the designation is designed to aid and expedite the regulatory process for investigational medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options.

SRSE

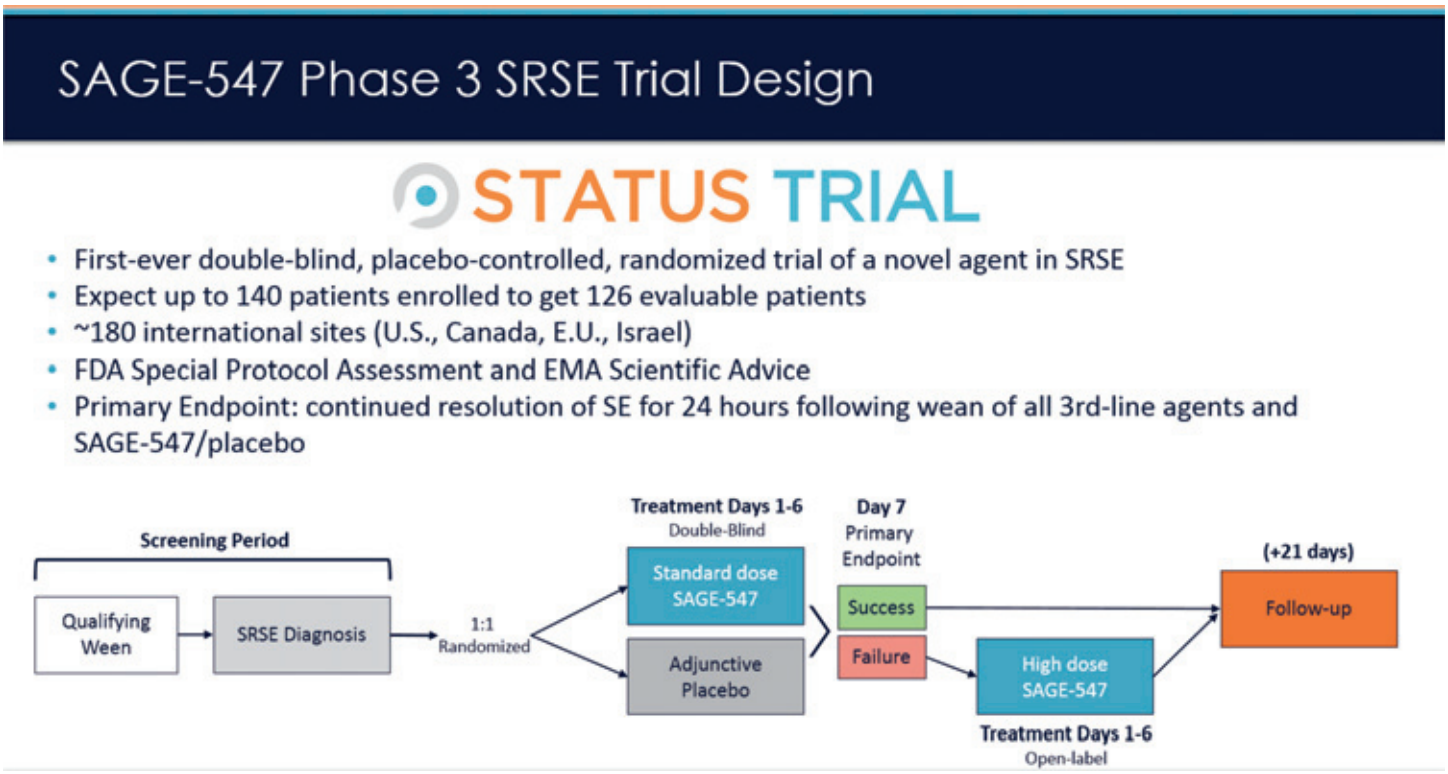
SRSE is rare, life-threatening condition where a patient is in a state of SE and all standard treatment regimens normally sufficient in stopping seizure activity have failed. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes, or recurrent seizures without regaining consciousness between seizures for greater than five minutes. Seizures are episodes of abnormal excessive or synchronous neuronal activity in the brain. Causes of SE include: low antiepileptic drug levels in patients with pre-existing epilepsy; cerebrovascular disease; metabolic and electrolyte disturbances; encephalopathies; head trauma; drug or substance intoxication; hypoxia; CNS infections; infectious diseases; genetic disorders or unknown causes.

An SE patient is first treated with BDZs and if no response, is then treated with other, second-line, anti-seizure drugs. If the seizure persists after second-line therapy, the patient is diagnosed as having refractory SE, or RSE, admitted to the intensive care unit, or ICU, and placed into a medically induced coma. RSE is commonly managed in the ICU by inducing either sustained seizure suppression or deeper near-complete electroencephalogram, or EEG, suppression, called "burst suppression", using continuous IV general anesthetics. The primary drugs used to induce coma are continuously infused IV agents such as propofol, midazolam or pentobarbital. The RSE patient is commonly monitored on a continuous basis through EEG to ensure sustained seizure suppression or burst suppression is achieved. The goal of sustained seizure suppression or burst suppression using continuous IV general anesthetics is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels. After a short period, typically 24 hours, physicians attempt to wean the patient from the medically induced coma to evaluate EEG activity to assess if the neuronal activity has returned to normal levels. If unsuccessful, the patient is placed back into the medically induced coma in order to protect underlying neurological activity and brain function. At this point, patients are considered to be in a state of SRSE. The current standard of care for SRSE is empiric, and there are no therapies at present that have been specifically approved for this indication. We estimate that there are between 25,000 and 41,000 cases of SRSE each year in the U.S.



Clinical Trials of SAGE-547 in SRSE

We are currently conducting the STATUS Trial, a global, randomized, double-blind, placebo-controlled Phase 3 clinical trial, to evaluate SAGE-547 as a treatment for patients with SRSE. We expect to enroll up to 140 patients, ages two and above, in the STATUS trial in order to obtain an estimated 126 evaluable patients. We anticipate that we will qualify approximately 180 sites in the U.S., Canada and Europe. The trial design, endpoints and statistical analysis approach for the trial are based on an agreement we reached with the FDA under a Special Protocol Assessment. Subjects are being randomized in a 1:1 ratio to receive either SAGE-547 or placebo in addition to standard-of-care third-line anti-seizure agents for six days. The primary efficacy endpoint of the trial is continued resolution of SE for 24 hours following wean of all third-line agents and the blinded study drug (SAGE-547 or placebo). Patients who do not respond during the initial treatment period are eligible for open-labeled treatment with SAGE-547.



We expect to report top-line results from this trial in the first half of 2017. If successful, we believe the results from this Phase 3 clinical trial, together with other data obtained from the SAGE-547 development program, will be sufficient to form the basis of an NDA submission for SAGE-547 in SRSE in the U.S. The FDA has granted us orphan drug designation for SAGE-547 in the treatment of SE including SRSE, and Fast Track designation for our IND for SAGE-547 as a treatment for SRSE. Based on scientific advice we received in the fourth quarter of 2016 from the EMA, we also believe our current Phase 3 program, if successful, will be sufficient to support an MAA submission to the EMA seeking approval of SAGE-547 for SRSE in the EU.

On May 14, 2015, we reported final results from our open-label Phase 1/2 clinical trial of SAGE-547 in SRSE. In the Phase 1/2 clinical trial, 17 of 22 (77%) evaluable patients met the key efficacy endpoint of being successfully weaned off their anesthetic agents while SAGE-547 was being administered at the maintenance dose. Subsequent post-hoc analysis involving duration of the weaning period (five days versus six days) showed that 16 of 22 (73%) evaluable subjects were successfully weaned off both anesthetic agents and SAGE-547 within five days of starting the SAGE-547 infusion without the need to reinstate anesthetic agents in the following 24-hour period, while 18 of 22 (82%) evaluable subjects were weaned off both anesthetic agents and SAGE-547 within six days of starting the SAGE-547 infusion without the need to reinstate anesthetic agents in the following 24-hour period which is the key efficacy endpoint of the ongoing Phase 3 clinical trial. SAGE-547 also showed favorable tolerability and a benefit-risk profile supporting further development for this acutely ill patient population. Overall, 64% of the 25 patients enrolled in the trial experienced at least one serious adverse event, though none were deemed drug-related as determined by the Safety Review Committee. Independent of treatment response, six patient deaths occurred within the study period, all driven by underlying medical conditions. Safety and tolerability were assessed by monitoring adverse events, EEG, physical examinations, neurological examinations, vital signs, clinical laboratory measures, electrocardiograms and concomitant medication usage. In order to allow full assessment of pharmacologic activity, the trial employed broad inclusion criteria, primarily excluding patients only if there is major damage to the brain, such as anoxic injury, devastating stroke or the presence of a large lesion. Other secondary objectives used to measure efficacy included scores on global and specific scales relating to cognition, agitation and depth of coma and survival. We can provide no assurance that the positive results observed in the Phase 1/2 trial will be replicated in the ongoing Phase 3 clinical trial.

We also expect to continue enrollment in a Phase 3 open-label expanded access trial, designated Study 302, which was initiated in April 2015. Study 302 is designed to make SAGE-547 available to patients in the U.S. who are affected by SRSE, but who have not been admitted to, nor can be transferred to, a STATUS trial site.

PPD

PPD is a distinct and readily identified major depressive disorder affecting an estimated 10-20% of women in the U.S. after childbirth, of whom an estimated 80% have moderate to severe symptoms. PPD is the most common biological complication of

childbirth, and is characterized by symptoms that often include sadness and depressed mood; anxiety or agitation; loss of interest in daily activities; changes in eating and sleeping habits; feeling overwhelmed; fatigue and decreased energy; inability to concentrate; hypervigilance about the baby or lack of interest in the newborn; and feelings of worthlessness, shame or guilt, which can lead to significant functional impairment. Without sufficient treatment, PPD may inhibit the mother's ability to perform daily activities and to bond with the baby and other members of the family. PPD also carries an increased risk for suicide in some women. Onset of moderate or severe symptoms is typically in the third trimester of pregnancy or within 4 weeks after giving birth. Current standard of care for PPD comprises psychotherapy, and in some cases, the cautious use of pharmacological therapies such as selective serotonin reuptake inhibitors, or SSRIs and serotonin and norepinephrine reuptake inhibitors, or SNRIs. Women with severe PPD may be hospitalized to provide a safe and stable environment for recovery if they have suicidal ideation or attempt, are unable to function and care for themselves, or require monitoring during a change in or trial of a new medication. There are no current approved therapies specifically for PPD. Naturally occurring allopregnanolone is found at its highest levels in women during the third trimester of pregnancy, returning to normal levels generally within 24 hours of giving birth. Levels of allopregnanolone have been found to be lower in women with PPD than in healthy women. Data also suggest that women with PPD may be unusually sensitive to the rapid decline in allopregnanolone, potentially causing $GABA_A$ -system mediated mood disruption. Given these data, we believe that allosteric modulators of the $GABA_A$ receptor may have potential in the treatment of PPD.

Clinical Trials of SAGE-547 in PPD

The Phase 3 Hummingbird Study of SAGE-547 in PPD commenced in the third quarter of 2016 as an extension of the Phase 2 clinical study. The Hummingbird Study is comprised of a randomized, placebo-controlled dose-ranging clinical trial of SAGE-547 in patients with severe PPD (202B) and a randomized, placebo-controlled clinical trial to evaluate SAGE-547 efficacy and safety in patients with moderate PPD (202C). We received Breakthrough Therapy Designation from the FDA for SAGE-547 in PPD in the third quarter of 2016. Breakthrough Therapy Designation is intended to offer a potentially expedited development path and review for promising drug candidates, which includes increased interaction and guidance from the FDA. In the fourth quarter of 2016, we announced input from an FDA Breakthrough Designation meeting confirming that the Hummingbird Study, with minor modifications, including increased sample size, is considered a Phase 3 clinical trial. We expect to enroll 120 patients with severe PPD in part 202B of the Hummingbird Study, with patients randomized 1:1:1 to receive either 60 mcg/kg/h or 90 mcg/kg/h of SAGE-547 or placebo (40 per group), and to enroll 100 patients with moderate PPD in part 202C of the Hummingbird Study, with patients randomized 1:1 to receive 90 mcg/kg/h of SAGE-547 or placebo (50 per group). We anticipate announcing top-line data from the Hummingbird Study in the second half of 2017. Based on the input we received from the FDA during the Breakthrough Designation meeting, we believe that, if successful, the results of the Hummingbird Study, together with the results of prior clinical studies of SAGE-547 in PPD, and ongoing non-clinical studies, will be sufficient to support the submission of an NDA to the FDA for SAGE-547 in the treatment of PPD. Additional patient safety data may be acquired through an open-label program. In the fourth quarter of 2016, we also received PRIME designation from the EMA for SAGE-547 in the treatment of PPD. The PRIME program was launched by the EMA in March 2016, and the designation is designed to aid and expedite the regulatory process for investigational medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. To be accepted, an investigational medicine must show the potential to benefit patients with unmet medical needs based on early clinical data. Once an investigational candidate has been selected for PRIME, developers are assigned a dedicated contact point and a rapporteur from the Committee for Medicinal Products for Human Use, or CHMP, to provide continuous support and help ahead of a marketing-authorization application, as well as a meeting with a multidisciplinary group of experts to provide broader guidance on the overall development plan and regulatory strategy. Companies who receive PRIME designation for a product candidate in an indication are also eligible for accelerated assessment at the time of their regulatory application.

In the third quarter of 2016, we announced positive top-line results from our multi-center, placebo-controlled, double-blind Phase 2 clinical trial of SAGE-547 for the treatment of severe PPD. Twenty-one patients were enrolled in the Phase 2 clinical trial. Patients were required to have had a major depressive episode that began no earlier than the third trimester and no later than the first four weeks following delivery, and also to be less than six months postpartum at the time of enrollment. Trial participants were also required to have a Hamilton Rating Scale for Depression, or HAM-D, score of 26 or above prior to treatment. In the trial, SAGE-547 achieved the primary endpoint of a significant reduction in the HAM-D compared to placebo at 60 hours ($p=0.008$). In the trial, there was a greater than 20 point mean reduction in the depression scores of the SAGE-547 group at 60 hours through completion of the trial with a greater than 12 point difference from placebo. The statistically significant difference in treatment effect began at 24 hours ($p=0.006$) with an effect that was maintained at similar magnitude through to the 30-day follow-up period ($p=0.01$). Remission from depression, as determined by a HAM-D <7, measured at 60 hours, was seen in 7 of 10 of the SAGE-547 group compared with 1 of 11 in the placebo group. Similarly, at 30 days, 7 of 10 of the SAGE-547 group and 2 of 11 in the placebo group were in remission. SAGE-547 was found to be generally well-tolerated. There were no deaths, serious adverse events or discontinuations due to adverse events.

The results of the Phase 2 PPD trial replicated and extended the findings of an earlier open-label probe study of SAGE-547 in severe PPD reported in 2015 that indicated a statistically significant improvement from baseline in depression in four women within 24 hours after administration of intravenous SAGE-547. During the SAGE-547 treatment period, all four patients rapidly achieved remission, as measured by HAM-D, and improved from a mean HAM-D score of 26.5 at baseline to a mean HAM-D score of 1.8 at the end of the 60-hour treatment period. All four patients also demonstrated consistent improvement as measured by the Clinical Global Impression-Improvement, or CGI-I scale. SAGE-547 was well-tolerated in all patients treated with no serious adverse events observed on therapy or during the 30-day follow-up period, and no discontinuations due to adverse events. A total of 14 adverse events were reported in four patients. The only adverse event reported in more than one patient was sedation (sleepiness) observed in two patients, which led to a decrease in dose.

SAGE-217

Overview

SAGE-217 is a novel neuroactive steroid that is a positive allosteric modulator of $GABA_A$ receptors. Like SAGE-547, SAGE-217 targets synaptic and extrasynaptic $GABA_A$ receptors. Our Phase 2 clinical program is focused on studying SAGE-217 in four indications: two movement disorder indications, essential tremor and Parkinson's disease, and two mood disorder indications, MDD and PPD. While SAGE-547 is an IV infusion intended for acute administration, SAGE-217 is currently being studied as an oral solution. We are in the process of developing solid oral dosage forms of SAGE-217 which we plan to introduce into our Phase 2 clinical program in the first half of 2017.

Proof-of-Concept and Phase 1

Given the similar mechanism of action of SAGE-217 to SAGE-547 as a modulator of the $GABA_A$ receptor, the selection of mood and movement disorders as initial indications for development of SAGE-217 was determined based, in part, on the results of completed clinical trials of SAGE-547 in PPD, as described above, and the results of a proof-of-concept clinical trial of SAGE-547 in essential tremor completed in 2015. In the randomized, double-blind, placebo-controlled, crossover trial of 25 patients affected by essential tremor, where patients were exposed to the target steady state dose of SAGE-547 for only two hours, several clinician-rated and accelerometer-rated measures showed significant reductions in tremor. These changes included a statistically significant reduction in accelerometer-measured upper limb kinetic tremor ($p=0.046$) which is one of the major manifestations of tremor impacting morbidity. Likewise, clinician ratings of large tremor motions, as well as smaller movements such as writing and spiral drawing, also showed improvement approaching statistical significance ($p=0.056$). In addition, SAGE-547 demonstrated a clinically meaningful reduction of tremor amplitude as measured by accelerometer (at least a 30% reduction from baseline) in 33% of patients, compared with 16% of patients in the placebo arm. In this phase of the trial, anti-tremor activity of SAGE-547 was observed at non-sedating doses, and peak anti-tremor activity correlated with steady state SAGE-547 levels. The time points showing the greatest reductions in tremor corresponded to peak plasma measurements. Seventeen of these patients were exposed to higher doses of SAGE-547 in an open-label extension with 44% demonstrating at least a 30% reduction in tremor amplitude from baseline. The most common adverse events at higher doses were fatigue and dizziness. Hypotension led to discontinuation of one patient. No serious adverse events were observed on therapy or during the 30-day follow-up period.

In the second quarter of 2016, we announced positive top-line results of a Phase 1 clinical program of SAGE-217. In the trial, SAGE-217 was found to be generally well-tolerated with no serious adverse events reported during the treatment and follow-up periods. Assessment of electrical activity in the brain using an EEG, showed clear evidence of target engagement ($GABA_A$ receptor modulation) starting at the lowest dose tested (15 mg). The observed EEG effect was sustained throughout the 7-day dosing period without diminution. Rates of moderate to deep sedation defined by a structured rating scale (MOAA/S < 3) were comparable to placebo until the maximum tolerated dose (MTD) was reached, in both the single and multiple ascending dose phases of the trial. The presence of sedation was associated with maximum drug exposure. As part of the Phase 1 clinical program, the safety, tolerability and pharmacokinetics of SAGE-217 were also studied in a small open-label cohort of essential tremor patients (n=6). While not designed to demonstrate efficacy, preliminary data show that single doses of SAGE-217 resulted in a similar reduction in tremor symptoms as achieved with a single 12 hour infusion of SAGE-547 in our previous placebo-controlled probe study (n=25).

SAGE-217 Mood Disorder Programs

Our SAGE-217 clinical program in mood disorders is comprised of Phase 2 clinical trials in MDD and PPD.

MDD is a condition in which a patient experiences at least two weeks of a major depressive episode which causes significant distress or disability where the episode is not due to medical or substance use and there is no history of mania or hypomania. In typical depressive episodes, the person experiences depressed mood, loss of interest and enjoyment, and reduced energy leading to diminished activity for at least two weeks. Many people with depression also suffer from anxiety symptoms and medically unexplained somatic symptoms. A person with moderate or severe MDD will typically have difficulties carrying out his or her usual work, school, domestic or social activities due to symptoms of depression. Antidepressants are widely used in the treatment of MDD,

but many patients do not adequately respond to existing treatments. According to estimates, approximately 16 million adults in the U.S. reported one major depressive episode in 2015. Preclinical and clinical evidence suggest the role of $GABA_A$ receptor dysfunction in depression. Low GABA and allopregnanolone levels have been found in the brain, cerebrospinal fluid and plasma of depressed patients. Our SAGE-217 MDD program is a two-part Phase 2a clinical trial evaluating the safety, tolerability, pharmacokinetics and efficacy of SAGE-217 in moderate to severe MDD patients. In February 2017, we announced top-line results from the open-label proof-of-concept portion (Part A) of the Phase 2 clinical trial evaluating SAGE-217 in 13 MDD patients. The primary endpoint of Part A was to evaluate safety and tolerability. SAGE-217 was found to be generally well-tolerated with no serious adverse events or discontinuations reported. The most common adverse events were sedation/somnolence, headache, dizziness, and myalgia. The trial also examined the effect of SAGE-217 on the HAM-D total score, in addition to other secondary measures. Patients in the trial had a mean HAM-D total score of 27.2 at baseline. Data demonstrated a mean reduction from baseline in the HAM-D of 19.9 points at Day 15, with 85% (11 of 13) patients showing at least a 50% reduction of their HAM-D and 62% (8 of 13) of patients achieving remission, as determined by a HAM-D $\leq$7. Statistically significant mean change from baseline was observed by Day 2 of the study, following the first of once-daily, nighttime oral dosing of 30 mg of SAGE-217. A significant mean change from baseline was maintained throughout the treatment period ($p<0.0001$ at Day 15). The reduction from baseline in depression ratings seen in Part A of the trial, met our criteria for advancing SAGE-217 into the double-blind, placebo-controlled portion of the Phase 2 clinical trial (Part B). We expect to initiate Part B of the Phase 2 clinical trial in the second quarter of 2017.

As discussed above, data suggest that women with PPD may be unusually sensitive to this rapid decline in allopregnanolone, potentially causing $GABA_A$-system mediated mood disruption. Given this data, we believe that allosteric modulators of the $GABA_A$ receptor may have potential in the treatment of PPD. Our Phase 2 clinical trial of SAGE-217 in PPD is a Phase 2a double-blind, placebo-controlled, randomized trial that will evaluate the efficacy, safety, tolerability and pharmacokinetics of SAGE-217 in approximately 32 patients with severe PPD. The primary endpoint of the trial is evaluation of the effect of SAGE-217 compared to placebo following two weeks of treatment as measured by the HAM-D total score. We expect to report top-line results from the SAGE-217 Phase 2 PPD trial in the second half of 2017.

SAGE-217 Movement Disorder Program

Our SAGE-217 clinical program in movement disorders is comprised of Phase 2 clinical trials in essential tremor and Parkinson's disease.

Essential tremor is one of the most common neurological disorders. It is a non-life threatening, chronic, progressive disorder associated with involuntary, rhythmic shaking in the upper limbs and head that can cause substantial disability. Some cases of essential tremor are inherited, and for others there is no known cause. We estimate that essential tremor affects approximately six to seven million people in the U.S., a significant portion of whom are thought to be undiagnosed and untreated. We estimate that approximately 1.5 million of those essential tremor patients have moderate to severe symptoms. Common pharmacological treatments for essential tremor include primidone; propranolol; anti-anxiety medications; and anticonvulsant drugs such as gabapentin and BDZs. Current treatments are only moderately effective, reducing, but not resolving, tremor amplitudes in approximately 50% of patients. Non-pharmaceutical interventions in the treatment of essential tremor include the responsible use of alcohol, deep brain stimulation, focused ultrasound and thalamotomy. Data suggest that essential tremor is associated with brain neurodegeneration, and $GABA_A$ receptor dysfunction, thus providing a rationale for studying compounds that are allosteric modulators of the $GABA_A$ receptor and show anti-convulsant activity as potential treatments for essential tremor. We are currently studying the efficacy, safety, tolerability and pharmacokinetics of SAGE-217 in a Phase 2a double-blind, placebo-controlled, randomized withdrawal trial of approximately 80 patients with essential tremor. The primary endpoint of the trial is to compare the effect of one week of SAGE-217 on overall kinetic tremor symptoms. Secondary endpoints include additional accelerometer-derived and clinician-rated rating scales. We expect to report top-line results from the Phase 2 clinical trial of SAGE-217 in essential tremor in the second half of 2017.

Parkinson's disease is a progressive neurodegenerative disorder associated with motor and non-motor symptoms, including resting tremor, and mood disorders. We estimate that Parkinson's disease affects an estimated 700,000 patients in the U.S, with an estimated 60,000 new cases each year. Parkinson's disease is thought to be caused by a reduction of dopamine levels as a result of loss of dopamine producing cells in the brain. Dopamine plays a key role in smooth and coordinated muscle movements. Current treatments for Parkinson's disease include: levodopa/carbidopa, dopamine antagonists, MAO-B inhibitors and anticholinergics. The part of the brain that produced dopamine also produces high levels of allopregnanolone. Dopamine neurons are under control of the GABA system. Decreased levels of allopregnanolone have been measured in the plasma and cerebrospinal fluid of patients with Parkinson's disease. Given these data, we believe that allosteric modulators of the $GABA_A$ receptor may have potential in the treatment of Parkinson's disease. Our Parkinson's disease Phase 2 program is comprised of a two-part Phase 2 clinical trial evaluating the safety, tolerability, pharmacokinetics and efficacy of SAGE-217 in moderate Parkinson's disease patients. Part A of the Phase 2 trial is an open-label, proof-of-concept study evaluating SAGE-217 in approximately 10 patients which, if promising, may lead to the Part B randomized, placebo-controlled Phase 2 trial. The primary endpoint for the Part A study is evaluation of the safety and tolerability of SAGE-217. The secondary endpoint is evaluation of improvement in motor symptoms as assessed by the change from baseline after one week in the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 3 (Motor

Examination) total score. We expect to report top-line results from the Part A open-label study of SAGE-217 in Parkinson's disease in the first half of 2017.

SAGE-718

SAGE-718 is the first product candidate selected for development from our NMDA receptor modulator program. SAGE-718 is a novel oxysterol-based positive allosteric modulator of NMDA receptors. In 2013, our scientists and collaborators published an article in The Journal of Neuroscience describing data from animal studies demonstrating that 24(S)-Hydroxycholesterol (cerebrosterol), a naturally occurring oxysterol, shows potent and selective activity in animal models as a positive allosteric modulator of NMDA receptors acting at a novel oxysterol modulatory site. SAGE-718 has been designed to be a highly potent and selective modulator of NMDA receptors with an optimized pharmacokinetic profile intended to support oral dosing. SAGE-718 has demonstrated robust activity in preclinical models of NMDA receptor hypofunction. We are developing SAGE-718 with an initial development focus on Anti-NMDA Receptor Encephalitis and cerebrosterol (24S-HC) deficit disorders such as Smith-Lemli-Opitz Syndrome, or SLOS. Anti-NMDA Receptor Encephalitis, or ANRE, is a rare autoimmune disorder in which antibodies attack NMDA receptors. Symptoms of ANRE include a highly characteristic set of neuropsychiatric deficits, including cognitive and behavioral disturbances, movement disorders and loss of consciousness. SLOS is a rare metabolic disorder caused by a mutation in the DHCR7 (7-dehydrocholesterol reductase) gene which codes for an enzyme that is involved in the production of cholesterol in the brain. SLOS is associated with significantly decreased plasma levels of cerebrosterol, suggesting that normal oxysterol-based modulation of NMDA receptors is disrupted in these patients. People affected by SLOS are unable to make enough of the necessary cholesterol in the brain to support normal growth and development, and are affected by a broad range of neuropsychiatric and neurodevelopmental symptoms. We have completed IND-enabling non-clinical studies of SAGE-718, and plan to commence the Phase 1 clinical program in the first half of 2017.

Beyond SLOS and ANRE, we believe measuring levels of anti-NMDA antibodies or decreased cerebrosterol levels may represent biomarkers to identify for future study broader patient populations characterized by cognitive dysfunction and neuropsychiatric symptoms resulting from NMDA receptor dysfunction or hypofunction. Examples of these potential areas for future evaluation include certain types, aspects or subpopulations of a number of diseases such as depression, Alzheimer’s disease, attention deficit hyperactivity disorder, schizophrenia, Huntington’s disease, and neuropathic pain.

SAGE-105, SAGE-324 and SAGE-689

SAGE-105 and SAGE-324 are novel neuroactive steroids that, like SAGE-547 and SAGE-217, target synaptic and extrasynaptic $GABA_A$ receptors. In late 2016, we initiated non-clinical studies of SAGE-105 and SAGE-324 with a focus on orphan epilepsies and indications involving GABA hypofunction. Based on data generated with SAGE-217 showing dose-related anticonvulsant activity in multiple acute seizure and chronic epilepsy models, we plan to develop SAGE-105 or SAGE-324 as an oral therapy for rare neurologic conditions associated with high frequencies of seizures, such as Tuberous Sclerosis, Dravet, Rett, PCDH-19, Dup15q and Lennox-Gastaut syndromes, all of which have small patient populations and an unmet medical need for additional treatment options to treat the seizures.

SAGE-689 is a novel positive allosteric modulator of $GABA_A$ receptors shown to have anticonvulsant, anxiolytic and sedative properties in animal models. The characteristics of SAGE-689 include a wide therapeutic window to allow for modulation of the $GABA_A$ receptor without inducing deep anesthesia, and a short half-life to permit rapid onset and loss of activity. In 2015, we filed an IND for SAGE-689 with an intended focus on the treatment of SE patients whose seizures have not resolved after treatment with BDZs prior to the patient being placed in a medically-induced coma. In response to the IND, the FDA requested additional non-clinical study data prior to commencement of a Phase 1 clinical trial. We are in the process of assessing next steps for the SAGE-689 program, and are evaluating possible alternative formulations for SAGE-689.

Further Exploitation of $GABA_A$ and NMDA Receptors

We expect to continue to focus our research and development efforts on allosteric modulation of the $GABA_A$ and NMDA receptor systems in the brain. The $GABA_A$ and NMDA receptor systems are broadly accepted as impacting many psychiatric and neurological disorders, spanning disorders of mood, seizure, cognition, anxiety, sleep, pain, epilepsy, and movement disorders among others. We believe that we will have the opportunity to develop molecules from our internal portfolio to address a number of these disorders in the future. Our ability to identify and develop such novel CNS therapies is enabled by our proprietary chemistry platform that is centered, as a starting point, on knowledge of the chemical scaffolds of certain endogenous neuroactive steroid compounds. We believe our knowledge of the chemistry and activity of allosteric modulators allows us to efficiently design molecules with different

characteristics. This diversity enables us to regulate important properties such as half-life, brain penetration and receptor pharmacology to develop product candidates that have the potential for better selectivity, increased tolerability, and fewer off-target side effects than either current CNS therapies or previous therapies which have failed in development.

Our current focus will remain on those indications where we can independently develop and commercialize our products, if approved. We believe our broad potential pipeline lessens our reliance on the success of any one program. We believe our ability to design and develop novel molecules with distinct profiles and receptor subtype selectivity will also provide us, in the future, with an opportunity to create value by potentially partnering these assets with third parties who possess the development and commercialization capabilities to pursue these programs.

Manufacturing and Supply

We neither own nor operate, and currently have no plans to own or operate, any manufacturing facilities. We currently resource all of our non-clinical and clinical material supply through third party contract manufacturing organizations, or CMOs, and intend to buy all of our future commercial supplies from CMOs if our product candidates are approved.

We have established relationships with several CMOs under which the CMOs have manufactured non-clinical and clinical supplies of SAGE-547, SAGE-217 and SAGE-718 active pharmaceutical ingredient, or API, as well as drug product. All clinical supplies are manufactured under current Good Manufacturing Practices, or cGMP. Starting materials and key intermediates to support the production of these candidates are manufactured by other CMOs on a purchase order basis. We do not currently have arrangements in place for either long-term supply or redundant supply of bulk drug substance or drug product for any of our product candidates. It is our intent to put long-term supply agreements in place for commercial manufacturing at the appropriate time, and to mitigate potential commercial supply risks for any products that are approved in the future through inventory management and through exploring additional manufacturers to provide API and/or drug product.

We currently have sufficient SAGE-547 drug product on hand for our Phase 3 clinical trials in SRSE and PPD and ongoing non-clinical studies, and are working with our CMOs to prepare for validation and commercial manufacturing of SAGE-547. We currently have sufficient SAGE-217 drug substance on hand for our ongoing Phase 2 clinical trials using an oral solution as the dosage form. We are in the process of developing solid oral dosage forms of SAGE-217 which we plan to introduce into our Phase 2 clinical program in the first half of 2017.

SAGE-547, SAGE-217 and SAGE-718 are small molecules isolated as stable crystalline solids. We believe the syntheses of SAGE-547, SAGE-217 and SAGE-718 are reliable and reproducible from readily available starting materials, and the synthetic routes are amenable to large-scale manufacturing and do not require unusual equipment in the manufacturing process. The enantiomeric purity of SAGE-547, SAGE-217 and SAGE-718 is derived from starting materials that are obtained from natural sources. We expect to continue to identify and develop drug candidates that are amenable to cost-effective manufacturing at contract manufacturing facilities.

Research and Development

Research and development expenses for the years ended December 31, 2016, 2015 and 2014 were $120.8 million, $69.4 million and $24.1 million, respectively.

Sales and Marketing

Given our stage of development, we have not yet established a commercial organization or distribution capabilities, nor have we entered into any partnership or co-promotion arrangements with an established pharmaceutical company. We believe that we can successfully launch and commercialize SAGE-547 on our own in SRSE and PPD in the U.S. and Canada, if the product is approved for both indications, using a small and highly specialized sales force similar in size to sales forces that other companies have used to marketing products for orphan indications. We expect to focus our future sales and marketing efforts, if SAGE-547 is approved in both indications, on critical care specialists, neurologists, epileptologists and clinical pharmacologists, in the case of SRSE, and OB/GYNs, psychiatrists, select primary care physicians, clinics, home infusion companies, and group practices, in the case of PPD, and together approximately 1,200 target hospitals particularly tertiary care centers where there are ICUs and staff trained to treat SRSE and other areas in the hospital capable of treating PPD patients with IV infusions.

We may decide to establish agreements or alliances with one or more distributors or pharmaceutical company collaborators to develop and commercialize our products, if approved, particularly in certain territories outside the United States where we do not

believe it makes commercial sense for us to proceed on our own. We may also consider other partnering opportunities if we believe the partnering opportunity will add significant value to our efforts, including through capabilities, infrastructure, speed or financial contributions, particularly in areas such as depression and cognition that impact large patient populations, in each case depending on, among other things, the applicable indications, the expected development pathway and related costs, deal terms, our available resources and whether the transaction makes strategic sense.

Licenses

We have entered into several license agreements to support our various programs.

Washington University

In November 2013, we entered into a license agreement with Washington University, or WU. Under this agreement, and subject to certain rights of the U.S. government and rights retained by WU, WU granted to us an exclusive, worldwide license under certain patent rights to make, have made, sell, and offer for sale, use and import products covered by certain of its patent rights. WU's rights in patent applications disclosing and claiming SAGE-689 are included in this license agreement. Under this agreement, WU also granted us non-exclusive license under certain technical information and tangible research information to use such technical information and/or tangible research information to make, have made, sell, offer for sale, use and import products that embody or were made using a method or process covered in the technical information and/or tangible research information. The WU license also grants us a right to sublicense our licensed rights to third parties, provided each sublicensee enters into a written agreement with us with terms consistent with our agreement with WU. We must pay to WU a percentage of the revenue we receive from sublicensing our rights under this agreement, initially in the mid-teens and decreasing to the mid-single digits over time.

Pursuant to the WU license, we are required to use commercially reasonable efforts to continue active, diligent development of licensed products and to use commercially reasonable efforts to manufacture, promote and sell licensed products throughout the territory and in the field during the term of the agreement. We must deliver written reports to WU describing our progress no later than January 31 and July 31 of the first two calendar years of the agreement, and no later than January 31 of each calendar year thereafter.

We must pay to WU an annual maintenance fee until and including the year in which our first Phase 2 clinical trial is initiated, and we must make up to $0.7 million and $0.5 million in clinical development and regulatory milestones, respectively, to WU, for each licensed product, upon reaching certain milestones relating to the clinical development of our product candidates. The license agreement also requires us to make low single-digit royalty payments to WU in connection with the sales of licensed products.

The WU agreement will expire on a licensed product-by-licensed product basis upon the later of (i) the last day that at least one valid patent claim covering the licensed product exists, or (ii) the tenth anniversary of the day of the first commercial sale of the licensed product. We may terminate the WU agreement early for convenience upon providing WU with 90 days' written notice. WU may terminate this agreement early in the event of our failure to cure a material breach within the applicable cure period or our bankruptcy. In the event of early termination of this agreement before the expiration of the last to expire of the patent rights, we must immediately discontinue manufacture, sale and distribution of any licensed products.

CyDex Pharmaceuticals

In September 2015, we amended and restated our existing commercial license agreement with CyDex Pharmaceuticals, Inc., or CyDex. Under the terms of the commercial license agreement, as amended and restated, CyDex has granted us an exclusive license to CyDex's Captisol drug formulation technology and related intellectual property for the manufacture of pharmaceutical products incorporating SAGE-547 or SAGE-689, and the development and commercialization of the resulting products in the treatment, prevention or diagnosis of any disease or symptom in humans or animals other than (i) the ocular treatment of any disease or condition with a formulation, including a hormone; (ii) topical ocular treatment of inflammatory conditions; (iii) treatment and prophylaxis of fungal infections in humans; and (iv) any ocular treatment for retinal degeneration.

Pursuant to the CyDex license, we are required during the term of the agreement to use commercially reasonable efforts to continue active, diligent development of the licensed product, to seek regulatory approval of the licensed product and to commercialize the licensed product following regulatory approval. We must deliver periodic progress reports to CyDex.

We are obligated to make milestone payments under the amended and restated license agreement with CyDex based on the achievement of clinical development and regulatory milestones in the amount of $0.8 million in clinical milestones and $3.8 million in regulatory milestones for each of the first two fields with respect to SAGE-547; $1.3 million in clinical milestones and $8.5 million in regulatory milestones for each of the third and fourth fields with respect to SAGE-547; and $0.8 million in clinical milestones and

$1.8 million in regulatory milestones for one field with respect to SAGE-689. The CyDex license is perpetual until terminated. We may terminate the CyDex agreement for convenience upon providing 180 days' prior written notice to CyDex. Either party has the right to terminate the agreement for failure to cure a material breach in the applicable cure period.

We will also be required to pay royalties to CyDex on sales of SAGE-547 and SAGE-689, if successfully developed, in the low single digits based on levels of net sales. We are also party to a supply agreement with CyDex which was amended in September 2015 to cover the supply of CyDex's Captisol for use in the manufacture of products incorporating SAGE-689. Under the amended supply agreement with CyDex, we are also required to purchase all of our requirements for Captisol with respect to SAGE-547 and SAGE-689 from CyDex, and CyDex is required to supply us with Captisol for such purposes, subject to certain limitations.

University of California

In October 2013, we entered into a license agreement with The Regents of the University of California, or the Regents, which was amended in May 2014. Pursuant to this agreement, and subject to certain rights of the U.S. government and rights retained by the Regents, the Regents granted us a non-exclusive, non-transferable license under all personal property rights of the Regents covering the tangible personal property in an IND application package owned by the Regents, or the Data, and a specified quantity of cGMP grade allopregnanolone, or the Material, to (i) use the Data for reference or incorporation in an IND for the use of the Material as a treatment of SE, essential tremor and/or severe PPD and (ii) use the Material or modifications of the Material to develop a pharmaceutical formulation for clinical trials for SE, essential tremor and/or postpartum depression. The rights licensed to us are not sublicenseable.

Pursuant to this agreement, we are required to use commercially reasonable efforts to proceed with the development, manufacture and sale of one or more products containing allopregnanolone, a derived product under the agreement, for the treatment of SE, essential tremor and/or severe PPD. As of January 1, 2014, we must deliver written reports to the Regents describing our progress no later than 60 days subsequent to June 30 and December 31 of each fiscal year.

This agreement requires us to make up to $0.1 million in milestone payments in connection with the first derived product that meets the relevant milestones, and we must also pay royalties of less than 1% to the Regents for each derived product for a period of 15 years following the first commercial sale of such derived product. This agreement will terminate on the earlier to occur of (i) 27 years after the effective date or (ii) 15 years after the last-derived product is first commercially sold. We may terminate this agreement early for convenience upon providing 60 days' prior written notice to the Regents. The Regents may terminate this agreement early in the event of material default, including failure to provide timely progress reports, after the applicable cure period, or in the event of our bankruptcy. In the event of early termination of this agreement, we have the right to sell any partially made derived products for a period of 120 days from the date of termination, but would not otherwise have rights after termination under the licensed rights to make, have made, use, sell, have sold, offer for sale or import products containing allopregnanolone.

In June 2015, we entered into an exclusive license agreement with the Regents whereby we were granted an exclusive license to certain patent rights related to the use of allopregnanolone to treat various diseases. In exchange for such license, we paid an upfront payment of $50,000, and will make annual maintenance fees of $15,000 until the calendar year following the first sale, if any, of a licensed product. We are obligated to make milestone payments following the achievement of specified regulatory and sales milestones of up to $0.7 million and $2.0 million in the aggregate, respectively. Following the first sale, if any, of a licensed product, we are obligated to pay royalties at a low single digit percentage of net sales, if any, subject to specified minimum annual royalty amounts. Unless terminated by operation of law or by acts of the parties under the terms of the agreement, the license agreement will terminate when the last-to-expire patents or last-to-be abandoned patent applications expire, whichever is later.

Intellectual Property

We strive to protect the proprietary technology that we believe is important to our business, including seeking and maintaining patents intended to cover our product candidates and compositions, their methods of use and processes for their manufacture, and any other aspects of inventions that are commercially important to the development of our business. We may 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.

We plan to continue to expand our intellectual property estate by filing patent applications directed to compositions, methods of use, treatment and patient selection and formulations and manufacturing processes created or identified from our ongoing development of our product candidates. Our success will depend on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop and

maintain our proprietary position. We seek to obtain domestic and international patent protection, and endeavor to promptly file patent applications for new commercially valuable inventions.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and patent scope can be reinterpreted by the courts after issuance. Moreover, many jurisdictions, including the United States, permit third parties to challenge issued patents in administrative proceedings, which may result in further narrowing or even cancellation of patent claims. We cannot predict whether the patent applications we are currently pursuing, or may in the future pursue, will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months or potentially even longer, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by our issued patents, our pending patent applications or of patent applications we may file in the future. Moreover, we may have to participate in interference proceedings or derivation proceedings declared by the United States Patent and Trademark Office, or U.S. PTO, or similar proceedings outside the U.S., to determine priority of invention.

Patents

We currently have one issued patent covering the composition of matter of SAGE-217. We have received notices of allowances for genus and species claims covering SAGE-689 as well as for methods of use of SAGE-689. We have a portfolio of patent applications at various stages of prosecution that fall into three categories: (1) SAGE-547-related; (2) $GABA_A$ receptor modulators; including genus and species claims to SAGE-217, SAGE-105, SAGE-324 and SAGE-689; and (3) NMDA receptor modulators, including
SAGE-718.

We own six patent application families generally related to SAGE-547. One of these families includes a patent application having claims to compositions containing allopregnanolone and a cyclodextrin. The compositions can be used for the treatment of CNS disorders such as SRSE, PPD and traumatic brain injury. The second patent family includes patent applications having claims directed to methods of treating seizure disorders, such as SRSE, by administering allopregnanolone using particular dosing regimens or multiple dosage phases. Any U.S. patents that may issue from these families of patent applications would have a statutory expiration date in January and August of 2033, respectively. The applications are also pending in foreign countries, including Australia, Brazil, Canada, China, Europe, Hong Kong, Israel, Indian, Japan, Mexico, New Zealand, Russia, Singapore, and South Africa. Two additional families of patent applications include methods of treating essential tremor and depression such as PPD. Included in these patent applications are courses of treatment and dosage regimens. A fifth family of patent applications includes claims to deuterated neuroactive steroid compounds and compositions. A sixth family of patent applications includes claims to formulation and manufacturing of SAGE-547. Any U.S. patents that may issue from these families of patent applications would have a statutory expiration date in September 2035, April 2036, and June 2036, respectively. The time period for electing to pursue foreign patent protection for the inventions disclosed in these patent applications by filing national stage patent applications in individual jurisdictions has not yet expired, and we will need to decide whether and where to pursue ex-U.S. protection before expiration of the applicable deadlines.

In addition to the patent applications licensed from WU, we own 23 families of patent applications, resulting from work done exclusively by us and our contract research organizations, directed to additional GABA receptor modulating compounds beyond SAGE-547 and SAGE-689, including SAGE-217 and methods of using these compounds. Any U.S. patents that may issue from these patent applications would have a statutory expiration ranging from October 2032 to November 2036. For example, our issued patent covering the composition of SAGE-217 has a statutory expiration date of April 2034. We have pending within these families of patent applications genus and species claims to the majority of the other compounds in our $GABA_A$ receptor modulating compound collection. These families of patent applications are at various stages of patent prosecution and include families for which only provisional applications have been filed. The time period for electing to pursue foreign patent protection by filing national stage patent applications in individual jurisdictions has not yet expired for some of these patent families, and we will need to decide whether and where to pursue ex-U.S. protection before expiration of the applicable deadlines.

We have exclusively licensed a portfolio of patent applications owned by WU, which are directed to certain GABA receptor modulating compounds and methods of using these compounds, for example in anesthesia or treatment of GABA-related disorders. This portfolio includes seven families of patent applications. One of these seven families of patent applications is co-owned by us, and this co-owned family includes pending patent applications in the United States, Australia, Brazil, Canada, China, Europe, Israel, India, Japan, Korea, Mexico, New Zealand, Philippines, Russia, Singapore, and South Africa. This co-owned application discloses and claims SAGE-689 and its use in anesthesia or treatment of GABA-related disorders. Any U.S. patents that may issue from the

SAGE-689 patent family would have a statutory expiration date of December 2033. Claims generically and specifically covering SAGE-689 have been allowed.

We also own twenty families of applications directed to modulators of NMDA receptors. Fifteen of these families of patent applications are directed to compounds that modulate NMDA receptors, including SAGE-718, which can be used to treat NMDA receptor-related disorders such as CNS-related conditions. One of these families of patent applications is directed to using a naturally occurring compound as a biomarker for a subject who would benefit from treatment with a modulator of NMDA receptors. One of these families of patent applications is directed to using a modulator of NMDA receptors to treat a rare NMDA loss of function disorder. Any patents that may issue, if any, from these families of applications directed to modulators of NMDA receptors would have statutory expiration dates in September 2032 and October 2037.

Patent term

The base term of a U.S. patent is 20 years from the filing date of the earliest-filed non-provisional patent application from which the patent claims priority. The term of a U.S. patent can be lengthened by patent term adjustment, which compensates the owner of the patent for administrative delays at the U.S. PTO. In some cases, the term of a U.S. patent is shortened by terminal disclaimer that reduces its term to that of an earlier-expiring patent.

The term of a U.S. patent may be eligible for patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act, to account for at least some of the time the drug is under development and regulatory review after the patent is granted. With regard to a drug for which FDA approval is the first permitted marketing of the active ingredient, the Hatch-Waxman Act allows for extension of the term of one U.S. patent that includes at least one claim covering the composition of matter of an FDA-approved drug, an FDA-approved method of treatment using the drug, and/or a method of manufacturing the FDA-approved drug. The extended patent term cannot exceed the shorter of five years beyond the non-extended expiration of the patent or 14 years from the date of the FDA approval of the drug. Some foreign jurisdictions, including Europe and Japan, also have patent term extension provisions, which allow for extension of the term of a patent that covers a drug approved by the applicable foreign regulatory agency. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extension on patents covering those products, their methods of use, and/or methods of manufacture.

Trade secrets

In addition to patents, we may rely on trade secrets and know-how to develop and maintain our competitive position. Companies typically rely on trade secrets to protect aspects of their business that are not amenable to, or that they do not consider appropriate for, patent protection. We protect trade secrets, if any, and know-how by establishing confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and partners. These agreements provide that all confidential information developed or made known during the course of an individual or entity's relationship with us must be kept confidential during and after the relationship. These agreements also generally provide that all relevant inventions resulting from work performed for us or relating to our business and conceived or completed during the period of employment or assignment, as applicable, shall be our exclusive property. In addition, we take other appropriate precautions, such as physical and technological security measures, to guard against misappropriation of our proprietary information by third parties.

Competition

The biopharmaceuticals industry is highly competitive. There are many public and private 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 therapies that have been specifically approved for the treatment of SRSE. However, many products approved for other indications, including general anesthetics, ketamine and anti-seizure drugs, are used off-label for various stages of SE therapy, including in the treatment of SRSE. Additionally, though not indicated, acupuncture, hypothermia, and electroconvulsive therapy are sometimes also used prior to withdrawal of care for patients with SRSE.

There are also no pharmacological therapies specifically approved for the treatment of PPD. Current standard of care for PPD commonly consists of psychotherapy, however, patients with moderate or severe PPD are often prescribed anti-depressant medications such as SSRIs and SNRIs.

Current treatments for Parkinson's disease include levodopa/carbidopa, dopamine antagonists, MAO-B inhibitors and anticholinergics.

Common pharmacological treatments for essential tremor include primidone; propranolol; anti-anxiety medications; and anticonvulsant drugs such as gabapentin and benzodiazepines. Non-pharmaceutical interventions in the treatment of essential tremor include the responsible use of alcohol, deep brain stimulation, focused ultrasound and thalamotomy.

MDD patients are typically treated with a variety of anti-depressant medications such as SSRIs and SNRIs. A number of companies are developing product candidates intended for the treatment of MDD.

In the field of neuroactive steroids focused specifically on modulation of $GABA_A$ receptors, our principal competitor is Marinus Pharmaceuticals, Inc., or Marinus. Marinus is developing a form of ganaxolone, a known $GABA_A$ positive allosteric modulator neuroactive steroid. A number of companies are working to develop products targeted at the NMDA receptor, both antagonists and agonists.

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. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. If we are successful in developing and gaining approval of any of our product candidates, we expect competition in the indications we are pursuing will focus on efficacy, safety, convenience, availability, and price. 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.

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.

U.S. drug development

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or 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 a company 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 studies and testing, 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, or GLP, 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, or 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, or 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 accept the NDA filing 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.

The data required to support an NDA are 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. 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. 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 protocols 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 whether 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 to patients with the disease or disorder being studies 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 describing, among other details, 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 institutional review board, or 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 (typically 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.

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, findings from other studies, or any findings 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. Success in one phase does not mean that the results will be observed in subsequent phases. Each phase may involve multiple studies. 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, or 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, or 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, 2017, the user fee for an application requiring clinical data, such as an NDA, is approximately $2.1 million. PDUFA also imposes an annual product fee for human drugs of approximately $0.1 million and an annual establishment fee of approximately $0.6 million on facilities used to manufacture prescription drugs. Fee waivers or reductions are available in certain circumstances, including a waiver of the application

fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

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

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. Before approving an NDA, the FDA will generally conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether the facilities 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 process for 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 one or more additional pivotal Phase 3 clinical trials, 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 are 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 typically requires that certain contraindications, warnings or precautions be included in the product labeling, and 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, or 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 a REMS is required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States, but 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 EU 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.

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 includes 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, or 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, or 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, or the PDMA, a part of the FDCA.

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 and 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 company marketing a prescription drug (or a party acting on its behalf) to knowingly and willfully solicit, receive, offer, or pay any remuneration (including any kickback, bribe or rebate), directly or indirectly, in cash or in kind, that is intended to induce or reward

the referral of business, including the purchase or order, or recommending the purchase or order, of a particular drug, for which payment may be made in whole or in part 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 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, or HIPAA. A person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it. Moreover, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

Although we would not submit claims directly to payors, drug manufacturers can be held liable under the federal False Claims Act, which prohibits anyone from, among other things, knowingly presenting, or causing to be presented claims for payment to federal programs (including Medicare and Medicaid) that are false or fraudulent, or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim. The government may deem companies 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 $10,781 and $21,563 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.

Numerous other laws may apply to our products. 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. 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 handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act.

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 statutes, regulations or the interpretation of existing laws or 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 U.S. PTO, 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 then owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or 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 a full 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, or NCA, and one or more Ethics Committees, or 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.

In the EU, pediatric data or an approved Pediatric Investigation Plan, or PIP, or waiver, is required to have been approved by the European Medicines Agency, or EMA, prior to submission of a marketing authorization application to the EMA. In most EU countries, we are also required to have an approved PIP before we can begin enrolling pediatric patients in a clinical trial. We do not yet have an approved PIP for any of our product candidates.

European Union drug review and approval

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

The Community MA is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the 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 State 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, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or 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 a generic marketing authorization application 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.

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 applicable to a given country, we may not be able to obtain regulatory approval for our product candidates in such country if we choose to seek such approval, or 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

If we are successful in developing and gaining regulatory approval for our product candidates, sales of our products will be dependent on the availability and extent of coverage and reimbursement from third-party payors. In the United States, healthcare providers are reimbursed for covered services and products they use through Medicare, Medicaid, and other government healthcare programs as well as through 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 products 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. Changes in government legislation or regulation and changes in private third-party payors' policies toward reimbursement for our products, if successfully developed and approved, may reduce reimbursement of our products' costs to physicians, pharmacies, and distributors. 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 limit our net revenue and results for any products we commercialize in the future. Decreases in third-party reimbursement for our products or a decision by a third-party payor not to cover a product for which we received marketing approval could reduce physician usage of our products and have a material adverse effect on our sales, results of operations and financial condition.

The pricing and reimbursement environment for our products may change in the future and become more challenging due to, among other reasons, policies advanced by the new presidential administration, federal agencies, new healthcare legislation passed by Congress or fiscal challenges faced by all levels of government health administration authorities. The American Recovery and Reinvestment Act of 2009, or ARRA, for example, allocated new federal funding to compare the effectiveness of different treatments for the same condition. 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 are made to Congress. Although ARRA does not mandate the use of the results of comparative effectiveness studies for reimbursement purposes, it is not clear what effect, if any, the research will have on the sales of any products for which we receive marketing approval or on the reimbursement policies of public and private payors. It is possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of any product for which we receive marketing approval. For example, if third-party payors find our products not 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.

One of the goals of the federal Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to herein as ACA, was 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 expanded and increased industry rebates for drugs covered under Medicaid. The ACA also 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 $1,000 to $10,000 for each payment or ownership interest that is not timely, accurately, or completely reported (annual maximum of $150,000), and $10,000 to $100,000 for each knowing failure to report (annual maximum of $1 million). The reporting requirements apply only to manufacturers of products for which reimbursement is available under Medicare, Medicaid, or the Children's Health Insurance Program.

The new presidential administration has identified repeal and replacement of the ACA as one of its priorities. We do not know at this time what implications such an action would have on the current requirements or on our future business. Other health regulatory laws, such as the federal Anti-Kickback Statute and the federal civil False Claims Act, have been applied to marketing and other activities engaged in by pharmaceutical companies whose products are reimbursed by federal healthcare programs, and, in many cases, government investigations or private lawsuits under these laws have led such companies to enter settlements that include significant monetary and other penalties, We cannot predict the full impact of the laws described above on our business until we have a marketed product. Many states have adopted laws similar to the federal laws discussed above. Some of these state laws 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 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.

Other legislative changes relating to reimbursement have been proposed and adopted in the United States since the ACA was enacted. For example, beginning April 1, 2013, Medicare payments for all items and services under Part A and B, including drugs and biologicals, and most payments to plans under Medicare Part D were reduced by 2% under the sequestration (i.e., automatic spending reductions) required by the Budget Control Act of 2011, or BCA, as amended by the American Taxpayer Relief Act of 2012. The BCA requires sequestration for most federal programs, excluding Medicaid, Social Security, and certain other programs. Subsequent legislation extended the 2% reduction, on average, to 2025. As long as these cuts remain in effect, they could adversely impact payment for any products we may commercialize in the future. 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 many 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, if approved. Historically, products launched in the EU do not follow price structures of the United States, and generally prices tend to be significantly lower.

Employees

As of February 15, 2017, we employed 135 full-time employees, including 94 in research and development and 41 in general and administrative and no part-time employees. 34 of our employees hold M.D. or Ph.D. degrees. We have never had a work stoppage, and none of our employees is represented by a labor organization or under any collective-bargaining arrangements. We consider our employee relations to be good.

Facilities

Our corporate headquarters are located in Cambridge, Massachusetts, and consist of 22,067 square feet in a multi-tenant building under a lease that will expire on February 28, 2022. In May 2016, we entered into a separate lease under which, beginning on September 1, 2016, we rent 19,805 square feet of additional office space in a separate multi-tenant building. The lease for the additional space will also expire in February 2022.

We expect to lease additional space prior to the expiration of our leases to meet the needs of the business.

Legal Proceedings

As of the date of this Annual Report on Form 10-K, 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 financial position, results of operations or cash flows.

Corporate Information

We were incorporated under the laws of the state of Delaware on April 16, 2010 and commenced operations on January 19, 2011 as Sterogen Biopharma, Inc. On September 13, 2011, we changed our name to Sage Therapeutics, Inc. under our Second Amended and Restated Certificate of Incorporation. Our mailing address and executive offices are located at 215 First Street, Cambridge, Massachusetts and our telephone number at that address is (617) 299-8380. We maintain an Internet website at the following address: www.sagerx.com. The information on our website is not incorporated by reference in this annual report on Form 10-K or in any other filings we make with the Securities and Exchange Commission, or SEC.

We make available on or through our website certain reports and amendments to those reports that we file with or furnish to the SEC in accordance with the Securities Exchange Act of 1934, as amended. These include our annual reports on Form 10-K, our quarterly reports on Form 10-Q, and our current reports on Form 8-K, and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act. We make this information available on or through our website free of charge as soon as reasonably practicable after we electronically file the information with, or furnish it to, the SEC.

You may read and copy any materials we file with the SEC, at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet website that contains reports, proxy and information statements, and other information regarding us and other issuers that file electronically with the SEC. The SEC's Internet website address is http://www.sec.gov.

Item 1A. Risk Factors

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this Annual Report and in our other public filings before making an investment decision. Our business, prospects, financial condition, or operating results could be harmed by any of these risks, as well as other risks not currently known to us or that we currently consider immaterial. If any such risks or uncertainties actually occur, our business, financial condition or operating results could differ materially from the plans, projections and other forward-looking statements included in this Annual Report, including in the foregoing Business section and later in the section entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this report and in our other public filings and public statements. The trading price of our common stock could decline due to any of these risks, and as a result, our stockholders may lose all or part of their investment.

Risks Related to Product Development, Regulatory Approval and Commercialization

We depend heavily on the success of our current product candidates, of which SAGE-547 is in Phase 3 clinical development for super-refractory status epilepticus, or SRSE, and post-partum depression, or PPD; SAGE 217 is in Phase 2 clinical development for PPD, essential tremor, Parkinson's disease and major depressive disorder, or MDD; and other product candidates are at earlier stages. We cannot be certain that we will be able to complete, within the expected time-frames, our non-clinical studies or clinical trials, or to announce results on the time-lines we expect. We cannot be certain that we will be able to advance our product candidates into additional trials, or to successfully develop, or obtain regulatory approval for, or successfully commercialize, any of our product candidates.

We currently have no drug products for sale, and may never be able to successfully develop marketable drug products. Our business depends heavily on our ability to successfully complete non-clinical and clinical development of our current product candidates, and to obtain regulatory approval and successfully commercialize those product candidates. 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. Our lead product candidate, SAGE-547, is currently in Phase 3 clinical development for the treatment of SRSE and PPD; SAGE-217 is in Phase 2 clinical development for PPD, essential tremor, Parkinson's disease and MDD; and other product candidates are at earlier stages.

Drug development involves a high degree of risk. We may not be able to complete our clinical trials or announce results from our clinical trials on the time-lines we expect. For instance, we have experienced slower than expected enrollment and randomization of patients in our Phase 3 clinical trial in SRSE. We may encounter similar difficulties in our other trials, particularly in clinical trials where an in-patient stay in required. These types of delays can lead to delays in completion of a trial and announcement of results. Similarly, there is also the potential for slower than expected clinical site initiation, delays or problems in analyzing data, and the potential need for additional analysis or data or the need to enroll additional patients in any of our clinical trials. We may also encounter delays arising from unexpected adverse events in a trial or other unexpected hurdles or issues in the conduct of any trial.

We may not be able to demonstrate the efficacy and safety of our current product candidates or any other product candidate at each stage of clinical development. Changes in formulations of our product candidates, such as moving from oral solution to solid dosage form intended for chronic use, which we are planning to do with respect to SAGE-217 for the ongoing Phase 2 clinical program and later clinical trials, could delay development or require us to conduct additional clinical trials or non-clinical studies. The results of clinical trials or non-clinical studies of our product candidates at any stage may not support further development or may not be sufficient to obtain regulatory approval. 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 U.S. and in other countries where we intend to test and, if approved, market any product candidate. Drug development is a long, expensive and uncertain process, and delay or failure can occur at any stage of our clinical trials. Success in non-clinical studies or in earlier stage clinical trials may not be repeated or observed in ongoing or future studies involving the same compound or other product candidates. The drug development process can take many years, and may include post-marketing studies and surveillance, which will require the expenditure of substantial resources. Of the large number of drugs in development in the U.S., only a small percentage will successfully complete the U.S. Food and Drug Administration, or FDA, regulatory approval process and will be commercialized. Accordingly, even if we have the requisite financial resources, when needed, to continue to fund our development efforts, we cannot assure you that any of our product candidates will be successfully developed or commercialized.

We are not permitted to market our product candidates in the U.S. until we receive approval of a New Drug Application, or an NDA, from the FDA, or in any foreign countries until we receive the requisite marketing approval from such countries. Obtaining approval of an NDA in the U.S. or marketing approval in any country outside the U.S. is a complex, lengthy, expensive and uncertain

process, and the FDA and regulatory authorities outside the U.S. may delay, limit or deny approval of any of our product candidates for many reasons, including, among others:

- we may not be able to demonstrate, to the satisfaction of the FDA or other regulatory authorities that our product candidates are safe and effective in any indication and that the benefits outweigh the safety risks;
- the results of our non-clinical studies and clinical trials may be negative, or may not meet the level of statistical or clinical significance required by the FDA or regulatory authorities outside the U.S. for marketing approval, or the FDA or regulatory authorities outside the U.S. may disagree with our interpretation of data from our non-clinical studies and clinical trials, or may not accept data generated at our non-clinical studies and clinical trial sites;
- the FDA or regulatory authorities outside the U.S. may disagree with the number, design, size, conduct, or implementation of our non-clinical studies or clinical trials or changes in drug formulation used in our non-clinical studies or clinical trials even if the regulatory authorities have previously reviewed and commented on the design and details of our plans;
- the FDA or regulatory authorities outside the U.S. may require that we conduct additional non-clinical studies and clinical trials prior to approval or post-approval;
- the FDA or applicable foreign regulatory authorities may not approve the formulation, labeling or specifications of any of our product candidates;
- if our NDA, if and when submitted, is reviewed by an advisory committee, 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;
- if an NDA for one of our product candidates is submitted, the FDA may approve the product candidate for a more limited patient population than we expect;
- the FDA may require development of a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval or post-approval;
- the FDA or applicable foreign regulatory authorities may determine that the manufacturing processes or facilities of third-party contract manufacturers with which we contract do not conform to applicable requirements, including current Good Manufacturing Practices, or cGMPs; or
- the FDA or applicable foreign regulatory agencies may change their approval policies or adopt new regulations.

Even if we receive marketing approval for our product candidates, regulatory or other governmental authorities may still impose significant restrictions on our products, including restrictions on indicated uses or marketing, or may impose ongoing requirements for potentially costly post-approval studies. For example, if we are successful in our efforts to obtain approval of SAGE-547 and other product candidates, we expect that, prior to product launch, the U.S. Drug Enforcement Agency, or DEA, will need to determine the controlled substance schedule of SAGE-547 and possibly such other product candidates, taking into account the recommendation of the FDA. The process may delay our ability to market any such product if it is approved. Any of these factors, many of which are beyond our control, could jeopardize or delay our ability to obtain regulatory approval for and successfully market our product candidates. Any such setback would have a material adverse effect on our business and prospects.

We cannot be certain that the results of our ongoing Phase 3 clinical trials of SAGE-547 in SRSE and PPD will be sufficient to support the submission of an NDA or MAA for this product candidate in SRSE and PPD, and in any event we must obtain additional clinical and non-clinical data before an NDA or MAA may be submitted.

In general, the FDA requires two pivotal trials to support approval of an NDA, but in certain circumstances, will approve an NDA based on only one pivotal trial. The trial design, endpoints and statistical analysis approach for our Phase 3 clinical trial of SAGE-547 in SRSE are based on an agreement we reached with the FDA under a Special Protocol Assessment. As a result, if we are successful, we believe the results from the Phase 3 clinical trial, together with other safety and efficacy data from the SAGE-547 development program, could form the basis of an NDA submission with the FDA for SAGE-547 in the treatment of SRSE. Based on scientific advice we recently received from the European Medicines Agency, or EMA, we also believe our current Phase 3 clinical program in SRSE, if successful, will be sufficient to support a MAA submission to the EMA seeking approval of SAGE-547 for SRSE in the EU. However, depending upon the outcome of the Phase 3 clinical program and the other development activities under the current program, the FDA or EMA may, despite the earlier input and advice on our study design, require that we conduct additional clinical trials or additional non-clinical studies before we can submit an NDA or MAA for SAGE-547 in SRSE or in order to gain approval of an NDA or MAA.

Based on input we received from the FDA during a Breakthrough Therapy meeting for SAGE-547 in PPD, we also believe that, if successful, the results of the Phase 3 clinical program in PPD, together with the results of prior clinical studies and ongoing non-clinical studies, will be sufficient to support the submission of an NDA with the FDA seeking marketing approval for SAGE-547 in PPD. However, depending upon the outcome of the Phase 3 clinical program and the other development activities under the current program, the FDA may, despite the input we received at the Breakthrough Designation meeting and our current expectations, require that we conduct additional clinical trials or non-clinical studies before we can submit an NDA for SAGE-547 in PPD or in order to gain approval of the NDA in PPD. Similarly, since we do not yet have scientific advice from the EMA with respect to our SAGE-547 PPD program, we do not know whether the EMA will require additional pivotal trials or additional non-clinical studies before we can submit an MAA for SAGE-547 in PPD in the EU or in order to gain approval of an MAA in PPD.

Furthermore, we will need to complete several other clinical and non-clinical studies prior to submitting an NDA to the FDA, including studies to evaluate the pharmacokinetics and/or pharmacodynamics of SAGE-547 in special populations. If the results of these additional clinical and non-clinical studies are delayed or yield unanticipated results, it may delay or prevent the submission or approval of an NDA for SAGE-547 for both SRSE and PPD.

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

We have received Fast Track designation for our investigational new drug application, or IND, for SAGE-547 for the treatment of SRSE, and in the future we may seek Fast Track designation for other product candidates as well. If a product is intended for the treatment of a serious or life-altering condition and the product demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for the FDA Fast Track designation. We have also received Breakthrough Therapy designation in the U.S. and PRIME designation in the EU for SAGE-547 in the treatment of PPD. Fast Track designation, Breakthrough Therapy designation and PRIME designation do not necessarily lead to a faster development pathway or regulatory review process, and do not increase the likelihood of regulatory approval. The FDA may withdraw Fast Track designation or Breakthrough Therapy designation, and the EMA may withdraw PRIME designation, if the relevant agency believes that the designation is no longer supported by data from our clinical development programs.

The number of patients with the diseases and disorders for which we are developing our product candidates has not been established with precision. If the actual number of patients with the diseases or disorders we elect to pursue with our product candidates is smaller than we anticipate, we may encounter difficulties in enrolling patients in our clinical trials, thereby delaying or preventing development of our product candidates, and even if such product candidates are approved, our revenue and ability to achieve profitability may be materially adversely affected.

Our lead product, SAGE-547, is currently in Phase 3 development for the treatment of patients with SRSE and PPD. The number of patients suffering from these disorders is small. We also have Phase 2 clinical programs of our next generation product candidate, SAGE-217 in essential tremor, PPD, Parkinson's disease and MDD. There is no precise method of establishing the actual number of patients with any of these disorders in any geography over any time period. Moreover, SRSE is an acute episodic condition. If we are not able to identify patients at the time of SRSE onset, we will have difficulty completing our Phase 3 clinical trial. Given the small number of patients, and nature of the disease, it may also be difficult to identify PPD patients for clinical trials, particularly patients with severe PPD. With respect to many of the indications in which we are conducting trials or plan to develop our product candidates, we have or will provide estimates of the prevalence of the disease or disorder. Our estimates as to prevalence may not be accurate, and the actual prevalence or addressable patient population for some or all of those indications, or any other indication that we elect to pursue, may be significantly smaller than our estimates. In estimating the potential prevalence of indications we are pursuing, or may in the future pursue, including our estimates as to the prevalence of SRSE, PPD, essential tremor and Parkinson's disease, we apply assumptions to available information that may not prove to be accurate. In each case, there is a range of estimates in the published literature which include estimates within the range that are lower than our estimates. For example, there are estimates in the literature on the prevalence of SRSE, particularly from studies outside the U.S. that are significantly lower than our estimates. We believe that differences in prevalence rates for SRSE among studies in the published literature may be the result of: differences from country-to-country in the prevalence or rate of occurrence of the underlying conditions and disorders that cause SRSE; challenges in making an accurate diagnosis of SRSE, particularly in a patient population with multiple complications; limitations and variations in the diagnosis coding for these conditions; the small size of the populations studied in the literature; and differences and limitations in the analytical plans underlying the various published studies. Similarly, our estimates of the prevalence of PPD are higher than estimates reported in some of the published literature or results obtained from certain studies analyzing limited claims databases. We believe this difference is due to under-diagnosis of PPD as a result of lack of screening and under-reporting, and patients being reluctant to seek treatment in clinical practice. The actual number of patients with SRSE, PPD, essential tremor, Parkinson's disease, MDD or any other indication in which we elect to pursue development of our product candidates may, however, be significantly lower than we believe. If the actual number of patients with SRSE, PPD, essential tremor, Parkinson's disease, MDD or any other indication in which we elect to pursue development of our product candidates is lower than our estimates, we may experience difficulty in

enrolling patients in our clinical trials, thereby delaying development of our product candidates. A prevalence calculation is an estimate of the total number of patients with a disease or disorder or the rate of occurrence of a disease or disorder in a population. Even if our prevalence estimates are correct, our products, if approved, may be indicated for only a subset of patients with a particular disease or condition. In addition, the IV infusion mode of administration for SAGE-547 may further limit the number of PPD patients who will be treated with the product if it is ultimately approved. If any of our product candidates are approved and our prevalence estimates with respect to any indication or our market assumptions are not accurate, the markets for our product candidates for these indications may be smaller than we anticipate, which could limit our revenues and our ability to achieve profitability.

If serious adverse events or other undesirable side effects are identified during the use of SAGE-547, SAGE-217, or any of our other product candidates in clinical trials, emergency-use cases, investigator sponsored trials, expanded access programs, or non-clinical studies, it may adversely affect our development of such product candidates.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt non-clinical studies and clinical trials, or could make it more difficult for us to enroll patients in our clinical trials. If serious adverse events or other undesirable side effects, or unexpected characteristics of SAGE-547 or SAGE-217 or of any of our other product candidates are observed in clinical trials, emergency-use cases, investigator sponsored clinical trials, or non-clinical studies, further clinical development of such product candidate may be delayed or we may not be able to continue development of such product candidates at all or we may also need to discontinue development of other product candidates, and the occurrence of these events could have a material adverse effect on our business. Undesirable side effects caused by our product candidates could also result in the delay or denial of regulatory approval by the FDA or other regulatory authorities or in a more restrictive label than we expect.

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

Positive results from non-clinical studies and clinical trials, including proof-of-concept trials, of our product candidates may not necessarily be predictive of the results we may obtain from subsequent non-clinical studies or clinical trials using the same product candidate or other product candidates. For example, the positive results from our Phase 1/2 clinical trial of SAGE-547 in SRSE and results from earlier emergency use cases, may not be replicated in our ongoing Phase 3 clinical trial. Our Phase 3 clinical trial of SAGE-547 differs in important ways from the Phase 1/2 clinical trial, which could cause the outcome of the Phase 3 clinical trial to differ from the earlier stage clinical trial. The Phase 3 clinical trial of SAGE-547 is a placebo-controlled trial, while our Phase 1/2 clinical trial was open-label, and in our Phase 3 clinical trial an intent-to-treat statistical analysis, which is a more rigorous statistical analysis, will be employed in evaluating the Phase 3 data. In addition, the formulation of SAGE-547 we are using in our Phase 3 trial is somewhat different than the formulation used in the Phase 1/2 trial. We do not believe the change in formulation will negatively affect trial results, but we cannot be sure. Similarly, the results from our Phase 2 clinical trials of SAGE-547 in severe PPD may not be replicated in our ongoing Phase 3 clinical trial of SAGE-547 in PPD, which involves a greater number of patients and also includes a moderate PPD arm, or in the Phase 2 clinical trial of SAGE-217 in PPD. Similarly, proof-of-concept data generated with SAGE-547 in essential tremor may not be replicated in the Phase 2 clinical trial of SAGE-217 in essential tremor. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials after achieving positive results in early-stage development, and we cannot be certain that we will not face similar setbacks. These setbacks have been caused by, among other things, non-clinical findings made while clinical trials were underway or safety or efficacy observations made in non-clinical studies and clinical trials that are different than in earlier trials or studies, including previously unreported or otherwise unexpected adverse events. For example, we may observe safety issues in clinical studies of our product candidates that we did not observe or appreciate in earlier stage clinical studies or in non-clinical studies. The results from non-clinical animal models may not be replicated in clinical trials. Many drug candidates, including many targeting CNS disorders, with promising non-clinical profiles have failed to demonstrate similar safety, non-toxicity and efficacy in humans. Moreover, non-clinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in non-clinical studies and clinical trials nonetheless failed to obtain FDA approval. If we fail to produce positive results in our planned non-clinical studies or clinical trials of any of our product candidates, the development timeline and regulatory approval and commercialization prospects for our product candidates, and, correspondingly, our business and financial prospects, would be materially adversely affected.

Failures or delays in the commencement or completion of our ongoing and planned clinical trials of our product candidates could cause us not to meet our expected timelines or result in increased costs to us, and could delay, prevent or limit our ability to gain regulatory approval of any product candidate and generate revenue and continue our business.

Successful completion of clinical trials at each applicable stage of development is a prerequisite to submitting an NDA to the FDA and, consequently, the ultimate approval and commercial marketing of SAGE-547 for SRSE or PPD and SAGE-217 or any of

our other product candidates for the indications in which we develop them. We do not know whether any of our clinical trials will begin or be completed, and results announced, as planned or expected, if at all, as the commencement and completion of clinical trials and announcement of results 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 investigational new drug applications, or INDs that may be required;
- negative results from our ongoing non-clinical studies or clinical trials;
- challenges in identifying, recruiting and enrolling patients to participate in clinical trials, including, in the case of SAGE-547, challenges we face due to: the small size of the patient population and acute nature of SRSE; the lack of proximity of some patients to trial sites; the lack of an approved pediatric investigation plan which is required to be submitted to enroll pediatric patients in most EU countries; challenges in meeting regulatory and material requirements to commence clinical trials in countries outside the U.S.; eligibility criteria for the clinical trial; and challenges associated with the nature of the clinical trial protocol; the potential for some or all of the same issues with respect to SAGE-547 in PPD or with respect to SAGE-217 or our other product candidates with respect to future clinical trials or other issues with respect to any of our clinical trials, such as the availability of existing treatments for the relevant disease, the requirement for in-patient stays with respect to some of our trials; and competition from other clinical trial programs for similar indications, to delay enrollment of patients in existing or future clinical trials of our other product candidates;
- delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical trials, for example delays in the manufacturing of sufficient supply of finished drug product;
- difficulties obtaining Institutional Review Board, or IRB, approval, and equivalent approval for sites outside the U.S., to conduct a clinical trial at a prospective site or sites;
- delays or problems in analyzing data, or the need for additional analysis or data or the need to enroll additional patients;
- the occurrence of serious adverse events or unexpected drug-related side effects experienced by patients in a clinical trial or unexpected results in ongoing non-clinical studies;
- delays in validating any endpoints utilized in a clinical trial;
- our inability to satisfy the requirements of the FDA to commence clinical trials, including chemistry, manufacturing and control, or CMC, requirements, or other FDA requirements prior to the initiation of a clinical trial;
- the FDA and applicable regulatory authorities outside the U.S. disagreeing with our clinical trial design and our interpretation of data from clinical trials, or changing the requirements for approval even after the regulatory authority has reviewed and commented on the design for our clinical trials;
- reports from non-clinical or clinical testing of other CNS therapies that raise safety or efficacy concerns; and
- difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trials, lack of efficacy, side effects, personal issues or loss of interest.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. For example, in 2015, in response to an IND filed with respect to SAGE-689, the FDA requested additional non-clinical study data prior to commencement of a Phase 1 clinical trial. There is no guarantee that we will generate data to satisfy the FDA or commence a Phase 1 clinical trial with respect to SAGE-689. We are in the process of evaluating possible alternative formulations of SAGE-689. In addition, a clinical trial may be suspended or terminated by us, the FDA, the IRBs at the sites where the IRBs are overseeing a clinical trial, a data and safety monitoring board, or DSMB, overseeing the clinical trial at issue or other regulatory authorities due to a number of factors, including, among others:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a partial or full clinical hold;
- unforeseen safety issues, including any that could be identified in our ongoing non-clinical studies, or adverse side effects or lack of effectiveness identified in ongoing clinical trials;

- 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 or FDA guidance or unanticipated events during our non-clinical studies and clinical trials of our product candidates may occur, which may result in changes to non-clinical studies and clinical trial protocols or the need for additional non-clinical studies and clinical trials, which could result in increased costs to us and could delay our development timeline.

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

We rely, and expect that we will continue to rely, on third parties to conduct any clinical trials for our product candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our products, if approved, 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 of our product candidates. We enter into agreements with third-party CROs to provide monitors for and to manage data for our ongoing 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 does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with regulations and guidelines, including current Good Clinical Practices, or cGCPs, for conducting, monitoring, recording and reporting the results of clinical trials to ensure that the data and results are scientifically credible and accurate, and that the trial patients are adequately informed of the potential risks of participating in clinical trials. These regulations are enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any products in clinical development. The FDA enforces cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs or clinical sites 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 or applicable regulatory authorities outside the U.S. will determine that our clinical trials comply with cGCPs. In addition, our clinical trials must be conducted with product candidates produced under cGMPs regulations. Our failure or the failure of our CROs or contract manufacturers 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.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs. If CROs 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 or regulatory requirements or for other reasons, and we are unable to rely on clinical data collected, 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. In such an event, we believe that our financial results and the commercial prospects for our product candidates 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 our product candidates in the future.

We do not currently have, nor do we plan to acquire, the infrastructure or capability internally to manufacture supplies of our product candidates, or any future product candidates, for use in the conduct of our non-clinical studies and clinical trials, or for future commercial use, and we rely completely on third-party suppliers for both active drug substances and finished drug products.

We will rely on our contract manufacturers to manufacture registration batches of both active drug substances and finished drug products required for regulatory approval as well as validation batches required for commercial manufacture. We expect our contract manufacturers to comply with cGMPs in the manufacture of our products. The facilities used by our contract manufacturers to manufacture the active pharmaceutical ingredient and final drug product must typically 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 equivalent foreign regulatory submission to the applicable regulatory agency. 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, and pass regulatory inspections, 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 third-party 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 and obtain regulatory approval for our product candidates and to market any approved products in the future. Our reliance on contract manufacturers also exposes us to the possibility that they, or third parties with access to their facilities, will have access to and may appropriate our trade secrets or other proprietary information.

We do not have long-term supply agreements in place with our contract manufacturers, and each batch of our product candidates is individually contracted under a quality agreement, service agreement and purchase order. If our existing contract manufacturers are not willing to enter into long-term supply agreements, or are not willing or are unable to supply drug substance or drug product to us, and we engage new contract manufacturers, such contractor manufacturers must scale up the manufacturing process, complete validation batches, pass an inspection by the FDA and other applicable foreign regulatory agencies, and be approved by regulatory authorities as our manufacturer before we are able to use drug product or drug substance they manufacture for commercial purposes which could result in significant delays or gaps in product availability. We plan to continue to rely upon contract manufacturers to manufacture commercial quantities of our products, if approved. If we are unable to maintain arrangements for third-party manufacturing, or are unable to do so on commercially reasonable terms, or are unable to obtain timely regulatory approvals in connection with our contract manufacturers, we may not be able to successfully complete development of our product candidates or commercialize our products, if approved.

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

Even if we receive marketing approval for our product candidates in the U.S., we may never receive regulatory approval to market our product candidates outside of the U.S. In order to market any product outside of the U.S., 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. 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. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the U.S. as well as other risks. In particular, in many countries outside of the U.S., 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. Even if we are able to successfully develop our product candidates and obtain marketing approval in a country, we may not be able to obtain pricing and reimbursement approvals in such country at acceptable levels or at all, and any pricing and reimbursement approval we may obtain may be subject to onerous restrictions such as caps or other hurdles or restrictions on reimbursement. Failure to obtain marketing and pricing approval in countries outside the U.S. or any delay or other setback in obtaining

such approval would impair our ability to market our product candidates in such foreign markets. Any such impairment would reduce the size of our potential market, which could have a material adverse impact on our business, results of operations and prospects.

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

We do not currently have an infrastructure for the sales, marketing and distribution of pharmaceutical products. In order to market our product candidates, if approved by the FDA or any other regulatory body, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition and prospects will be materially adversely affected.

Even if we receive marketing approval for our product candidates, our approved products 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 approved products among the medical community, including physicians, patients and healthcare payors. Market acceptance of our products, if approved, will depend on a number of factors, including, among others:

- the efficacy of our products as demonstrated in clinical trials, and, if required by any applicable regulatory authority in connection with the approval for the applicable indications, our ability to demonstrate in clinical trials that our products provide patients with incremental health benefits, as compared with other available CNS therapies;
- limitations or warnings contained in the labeling approved for our products by the FDA or other applicable regulatory authorities;
- the clinical indications and size of patient populations for which our products are approved;
- availability of alternative treatments already approved or expected to be commercially launched in the near future;
- the potential and perceived advantages and limitations of our products, including in the case of SAGE-547 limitations arising from the IV infusion mode of administration, 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 approved products 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 or as co-pay amounts under third party coverage.

If our product candidates are approved, but do not achieve an adequate level of acceptance by patients, physicians and payors, or if the patient population for which any such product is approved is smaller than we expect, we may not generate sufficient revenue from our products 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 or healthcare costs savings. Our efforts to educate the medical community and third-party payors about the benefits of our products, if approved and to the extent permitted, may require significant resources and may never be successful.

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

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

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 products (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 products;
- regulatory authorities may require the addition of labeling statements, such as a "boxed" warning or a contraindication;
- we may be required to change the way such products are distributed or administered, conduct additional clinical trials or change the labeling of the products;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to remove such products 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 products, and could substantially increase the costs of commercializing our products and significantly impact our ability to successfully commercialize our products 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 products, indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. For example, if we are successful in our efforts to obtain approval of SAGE-547 and other product candidates, we expect that, prior to product launch, the DEA will need to determine the controlled substance schedule of SAGE-547, and possibly such other product candidates, taking into account the recommendation of the FDA. The process may delay our ability to market any such product if it is approved. Our products, if approved, 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 additional 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 products, if approved, such as adverse events of unanticipated severity or frequency, or problems with the facility where our products are manufactured, a regulatory agency may impose restrictions on our products, the manufacturer or us, including requiring withdrawal of such products from the market or suspension of manufacturing. If we, our product candidates or approved products or the manufacturing facilities for our product candidates or products fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications submitted by us;

- suspend or impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products, refuse to permit the import or export of products, or require that we initiate a product recall.

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

The biopharmaceuticals industry is highly competitive. There are many public and private 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 therapies that have been specifically approved for treatment of SRSE. However, many products approved for other indications, including general anesthetics, ketamine and anti-seizure drugs, are used off-label for various stages of SE therapy, including in the treatment of SRSE. Additionally, though not indicated, acupuncture, hypothermia, and electroconvulsive therapy are sometimes also used prior to withdrawal of care for patients with SRSE.

There are no pharmacological therapies specifically approved for the treatment of PPD. Current standard of care for PPD commonly consists of psychotherapy, however, patients with moderate or severe PPD are often prescribed anti-depressant medications such as selective serotonin reuptake inhibitors, or SSRIs and serotonin and norepinephrine reuptake inhibitors, or SNRIs.

Current treatments for Parkinson's disease include Levodopa/carbidopa, dopamine antagonists, MAO-B inhibitors and anticholinergics.

Common pharmacological treatments for essential tremor include primidone; propranolol; anti-anxiety medications; and anticonvulsant drugs such as gabapentin and benzodiazepines. Non-pharmaceutical interventions in the treatment of essential tremor include the responsible use of alcohol, deep brain stimulation, focused ultrasound and thalamotomy.

MDD patients are typically treated with a variety of anti-depressant medications, including SSRIs and SNRIs. A number of companies are developing product candidates intended for the treatment of MDD.

In the field of neuroactive steroids focused specifically on modulation of $GABA_A$ receptors, our principal competitor is Marinus Pharmaceuticals, Inc., or Marinus. Marinus is developing a form of ganaxolone, a known $GABA_A$ positive allosteric modulator neuroactive steroid. A number of companies are working to develop products targeted at the NMDA receptor, both antagonists and agonists.

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. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of our competitors. Even if we are successful in developing and gaining approval of any of our product candidates, we expect competition in the indications we are pursuing will focus on efficacy, safety, convenience, availability, and price. 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 or expand our internal efforts and growth.

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 in some or all markets.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the U.S., the potential market for the applicable 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 license 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 or unwilling 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 in some or all markets or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense, including potentially increasing our infrastructure and investment outside the U.S.. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue. In addition such efforts may require diversion of a disproportionate amount of our attention away from other day-to-day activities, and require devotion of a substantial amount of our time to managing these expansion activities.

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

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

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our proprietary chemistry platform. Although some of our product candidates are in non-clinical and clinical development, our research programs may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying additional potential product candidates or our potential product candidates may be shown to have harmful side effects or may not have a positive risk/benefit profile or may have other characteristics that may make the product candidates unmarketable or unlikely to receive marketing approval.

Because we have limited financial and management resources, we focus on a limited number of clinical and research programs and product candidates and are currently focused on certain CNS disorders. 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. 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. 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.

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 will be subject to additional healthcare statutory and regulatory requirements and enforcement by the federal government and the states and foreign governments in which we conduct our business. Healthcare providers, physicians and others will play a primary role in the recommendation and prescription of our product candidates, if approved. Our future arrangements with third-party payors will expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our product candidates, if we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- The federal anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid.
- The federal False Claims Act imposes criminal and civil penalties, including those from civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government.
- The federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information.
- The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services.
- The federal transparency requirements, sometimes referred to as the "Sunshine Act", under the Patient Protection and Affordable Care Act, require manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests.
- Analogous state laws and regulations, such as state anti-kickback and false claims laws and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and drug pricing.

Ensuring that our future business arrangements with third parties comply with applicable healthcare laws and regulations could be costly. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities to be conducted by our sales team, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines and exclusion from government funded healthcare programs, such as Medicare and Medicaid, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business are 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 and enforcement 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 and enforcement agencies strictly regulate the promotional claims that may be made about prescription products, if approved, and enforce laws and regulations prohibiting the promotion of off-label uses. 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 approved labeling of the product. If we are found to have promoted off-label uses for any product, 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.

SAGE-547 will, and our other product candidates may, contain controlled substances, the manufacture, use, sale, importation, exportation, prescribing and distribution of which are subject to regulation by the DEA.

Before we can commercialize SAGE-547, and potentially our other product candidates, it is expected that the DEA will need to determine the controlled substance schedule, taking into account the recommendation of the FDA. This could delay our marketing of a product candidate and could potentially shorten the benefit of any regulatory exclusivity periods for which we may be eligible. If approved, SAGE-547 is expected to be, and our other product candidates may be, regulated as "controlled substances" as defined in the Controlled Substances Act of 1970, or CSA, and the implementing regulations of the DEA, which establish registration, security, recordkeeping, reporting, storage, distribution, importation, exportation, inventory, quota and other requirements administered by the DEA. These requirements are applicable to us, to our third-party manufacturers and to distributors, prescribers and dispensers of our product candidates. The DEA regulates the handling of controlled substances through a closed chain of distribution. This control extends to the equipment and raw materials used in their manufacture and packaging, in order to prevent loss and diversion into illicit channels of commerce. A number of states and foreign countries also independently regulate these drugs as controlled substances.

The DEA regulates controlled substances as Schedule I, II, III, IV or V substances. Schedule I substances by definition have no established medicinal use, and may not be marketed or sold in the U.S. A pharmaceutical product may be listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest risk of abuse and Schedule V substances the lowest relative risk of abuse among such substances.

We expect that SAGE-547 will be, and our other product candidates may be, listed by the DEA as Schedule IV controlled substances under the CSA. Consequently, the manufacturing, shipping, storing, selling and using of the products will be subject to an additional regulation. Distribution, prescribing and dispensing of these drugs are also regulated. Other Schedule IV compounds include sedative hypnotics such as benzodiazepines.

Annual registration is required for any facility that manufactures, distributes, dispenses, imports or exports any controlled substance. The registration is specific to the particular location, activity and controlled substance schedule.

Because of their restrictive nature, these laws and regulations could limit commercialization of our product candidates containing controlled substances. Failure to comply with these laws and regulations could also result in withdrawal of our DEA registrations, disruption in manufacturing and distribution activities, consent decrees, criminal and civil penalties and state actions, among other consequences.

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. The pricing and reimbursement environment for our products may change in the future and become more challenging due to, among other reasons, policies advanced by the new presidential administration, federal agencies, new healthcare legislation passed by Congress or fiscal challenges faced by all levels of government health administration authorities. We cannot be sure that reimbursement will be available for our product candidates and, if reimbursement is available, the level of such reimbursement and whether patients will be required to try other therapies prior to being prescribed our product candidate. 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 many foreign countries, including 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 to twelve 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, if it is conditioned on unreasonable caps or rebates, or if pricing is set at unsatisfactory levels, our operating results could be materially adversely affected.

Even though we have obtained orphan drug designation for SAGE-547 as a treatment for SE, including SRSE in the U.S., there may be limits to the regulatory exclusivity afforded by such designation, and such exclusivity will not apply to any non-orphan indications for which SAGE-547 may be approved.

Even though we have obtained orphan drug designation for SAGE-547 for treatment of SE, including SRSE, from the FDA in the U.S., there are limitations to exclusivity afforded by such designation. In the U.S., 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 in such indication 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 approval for a drug that shares the same active moiety as an already approved orphan-designated 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 U.S. 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.

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 gain approval of, and commercialize, our product candidates in foreign markets for which we may rely on collaboration with third parties. If we are able to gain approval for, and commercialize our product candidates in foreign markets, we would be subject to additional risks and uncertainties, including:

- the amount of reimbursement for our product candidates in foreign markets, and the nature of any limitations and caps on such reimbursement;
- our inability to directly control commercial activities to the extent 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.

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 that are important to the development of our business. We may also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents, should they issue; preserve the confidentiality of our trade secrets; and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain the proprietary position of our product candidates. Our owned and licensed patent applications relate to formulations and methods of use of SAGE-547, and compositions and methods of use of certain other $GABA_A$ receptor modulators, including genus and species claims to SAGE-217, SAGE-105, SAGE-324 and SAGE-689 and NMDA receptor modulators, including SAGE-718. We have an issued patent covering the composition of matter of SAGE-217, as well as formulations and methods of use. We also have allowed genus and species claims covering SAGE-689 which we expect to issue in a patent.

We currently have one issued patent covering the composition of matter of SAGE-217. We do not have any other issued patents covering our lead product candidates, SAGE-547, SAGE-217, SAGE-718, SAGE 105, SAGE-324, or SAGE-689. We have received notices of allowance directed to genus and species claims covering SAGE-689 as well as for methods of use of SAGE-689. We cannot provide any assurances that any of our pending patent applications will mature into issued patents and, if they do, that such patents will include, claims with a scope sufficient to protect our product candidates or otherwise provide any competitive advantage. For example, the patent applications that may provide coverage for SAGE-547 only cover particular formulations and particular methods of using such formulations to treat seizure conditions, such as SRSE and to treat depressive disorders such as PPD and MDD. As a result, if a patent issues from such patent applications, it would not prevent third-party competitors from creating, making and marketing alternative formulations, that fall outside the scope of our patent claims or practicing alternative methods. There can be no assurance that any such alternative formulations will not be equally effective as our formulation of SAGE-547. Moreover, other parties have developed technologies that may be related or competitive to our approach, and may have filed or may file patent applications and may have received or may receive patents that may overlap or conflict with our patent applications, either by claiming the same methods or formulations or by claiming subject matter that could dominate our patent position. Such third-party patent positions may limit or even eliminate our ability to obtain patent protection for certain inventions.

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 U.S., 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 if any of our product candidates are approved in those countries.

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 pending patent applications, if issued as a patent, will include claims having a scope sufficient to protect our current product candidates or any other products or product candidates;
- any of our pending patent applications will issue as patents at all;
- we will be able to successfully commercialize our product candidates, if approved, before our relevant patents expire;
- we were the first to make the inventions covered by each of our pending patent applications and any patents that may issue in the future;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe any patents that may be issued to us;
- 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 may rely upon unpatented trade secrets, and depend on unpatented know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. It is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants who are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could otherwise become known or be independently discovered by our competitors.

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

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

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 products, competitors may claim that our technology infringes their intellectual property rights as part of business strategies designed to impede our successful commercialization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, third parties may have currently pending patent applications which may later result in issued patents that our product candidates may infringe, or which such third parties claim are infringed by our technologies. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we are sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid, and we may not be able to do this. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on us. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. Patent litigation is costly and time-consuming. Any claim relating to intellectual property infringement that is successfully

asserted against us may require us to pay substantial damages, including treble damages and attorney's fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing our product candidates. In the case of trademark claims, if we are found to be infringing, we may be required to 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. 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.

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 to us 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 or another party.

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

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

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

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 U.S.

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 U.S., defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *ex parte* reexamination, or *inter partes* 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 would be prohibitively expensive, and our intellectual property rights in some countries outside the U.S. could be less extensive than those in the U.S., assuming that rights are obtained in the U.S. 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 U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing products made using our inventions in and into the U.S. 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.

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 U.S. 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 U.S. 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. For example, an April 2014 report from the Office of the U.S. Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. 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 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 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 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 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 market products 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.

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 are parties to an exclusive license agreement with Washington University, or WU, under which we have licensed certain patent families that comprise a variety of small molecule allosteric modulators of $GABA_A$ receptors and for which we have the worldwide right to develop and commercialize. A patent family that discloses and claims SAGE-689 is licensed to us under this agreement. We are obligated to pay WU certain clinical/regulatory milestones and single-digit royalties on products developed from this technology. Termination of our license agreement with WU would have a material adverse impact on our ability to develop and commercialize SAGE-689.

We have also entered into an exclusive license agreement with CyDex Pharmaceuticals, Inc., or CyDex, a wholly owned subsidiary of Ligand Pharmaceuticals, Inc., to use its Captisol technology to develop SAGE-547 and SAGE-689 for the field of use, which includes all fields for the treatment, prevention or diagnosis of any disease or symptom in humans or animals other than (i) the ocular treatment of any disease or condition with a formulation, including a hormone; (ii) topical ocular treatment of inflammatory conditions; (iii) treatment and prophylaxis of fungal infections in humans; and (iv) any ocular treatment for retinal degeneration. We are obligated to pay CyDex certain clinical/regulatory milestones and, if approved and marketed, single-digit royalties on SAGE-547 and SAGE-689. In addition, we have entered into a supply agreement with CyDex, pursuant to which CyDex supplies us with Captisol to formulate both products. Absent an alternative agreement by the parties, our rights under our exclusive license agreement terminate in the event that the supply agreement terminates. Currently, our SAGE-547 and SAGE-689 product candidates are formulated in Captisol. Termination of our license agreement with CyDex would have a material adverse impact on our ability to develop and commercialize SAGE-547 and SAGE-689 in their current formulations.

We also entered into a non-exclusive license with The Regents of the University of California, or the Regents. Pursuant to this agreement the Regents granted us a non-exclusive, non-transferable license under all personal property rights of the Regents covering the tangible personal property in an IND application package owned by the Regents, or the Data, and a specified quantity of cGMP grade allopregnanolone, or the Material, to (i) use the Data for reference or incorporation in an IND for use of the Material as a treatment of SE, essential tremor and/or postpartum depression and (ii) use the Material or modifications of the Material to develop a pharmaceutical formulation for clinical trials for SE, essential tremor and/or postpartum depression. This agreement requires us to pay milestone payments in connection with the first derived product, which would include SAGE-547, that meets the relevant milestones and we must also pay single-digit royalties for each derived product for a period of 15 years following the first commercial sale of such derived product. Termination of our license agreement with the Regents would have a material adverse impact on our ability to develop and commercialize derived products, which would include SAGE-547.

In June 2015, we entered into an exclusive license agreement with the Regents under which we were granted an exclusive license to certain patent rights related to the use of allopregnanolone to treat various diseases. In exchange for such license, we paid an upfront payment and will pay annual maintenance fees until the calendar year following the first sale, if any, of a licensed product. We are obligated to make milestone payments following the achievement of specified regulatory and sales milestones. Following the first sale, if any, of a licensed product, we are obligated to pay royalties at a low single digit percentage of net sales, if any, of licensed products, subject to specified minimum annual royalty amounts.

We may enter into additional licenses to third-party intellectual property that are necessary or useful to our business. Our current licenses and any future licenses that we may enter into impose various royalty payment, milestone, and other obligations on us. For example, as is the case for the Washington University license, 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, the licensor may allege that we have breached our license agreement, and may accordingly seek to terminate our license. In addition, future licensors may decide to terminate their licenses with us 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 may have been generated through the use of U.S. government funding and may therefore be subject to certain federal regulations. For example, some of the intellectual property rights licensed to us under the license agreements with WU and the Regents may have been generated using U.S. government funds. 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, or 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 the government 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.

If we enter into future arrangements involving 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 if we do not obtain new chemical entity or other types of marketing and 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 future 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 SAGE-547, allopregnanolone, 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, and we do not have any other exclusivity, our competitors may obtain approval of competing products following our patent expiration, and our ability to generate revenues could be materially adversely affected.

Marketing exclusivity provisions under the Federal Food, Drug, and Cosmetic Act, or FDCA, can also delay the submission or the approval of certain marketing applications by other companies for a product with the same active moiety as a product we may in the future sell. 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, or NCE. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or 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 a full 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. Even if we are able to obtain NCE or data exclusivity under the FDCA, the applicable five-year and three-year exclusivity periods will not delay the submission or approval of a full NDA. There is also no guarantee that any of our product candidates will qualify for marketing or data exclusivity under these provisions or that such exclusivity will alone be sufficient to for our business. If we do not have adequate patent protection or other exclusivity for our products, our business, financial condition or results of operations could be 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 U.S. 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. On June 19, 2014 in *Alice Corporation Pty. Ltd. v. CLS Bank*

International, et al., a case involving patent claims directed to a method for mitigating settlement risk, the Court held that the patent eligibility of claims directed to abstract ideas, products of nature, and laws of nature should be determined using the same framework set forth in Prometheus. The U.S. PTO recently issued a set of guidelines setting forth procedures for determining subject matter eligibility of claims directed to abstract ideas, products of nature, and laws of nature in line with the Prometheus, Myriad, and Alice decisions. The guidance does not limit the application of Myriad to DNA but, rather, applies the decision to other natural products.

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

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

Most of our employees 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 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 may 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 develop and commercialize our product candidates, which would materially adversely affect our efforts and results.

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 any patents that have, or may, 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;
- third parties may assert an ownership interest in our intellectual property and, if successful, such disputes may preclude us from exercising exclusive rights over that intellectual property;
- we may not develop or in-license additional proprietary technologies that are patentable; 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.

General Company-Related Risks

As our product candidates reach later stage clinical development, we will need to develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.

As we plan for a potential commercial launch of our product candidates, if approved, we expect to continue to increase our number of employees and the scope of our operations. To successfully execute our activities, and to manage our anticipated expansion, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. In addition, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities, and devote a substantial amount of time to managing these expansion activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes or delays, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs, and may divert financial resources from other projects, such as the development of our product candidates. If our management is unable to effectively manage our expected expansion, our expenses may increase more than expected, and our ability to successfully develop and gain regulatory approval of our product candidates and generate or increase our revenue, if such product candidates are approved, could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future expansion of our company.

Our future success depends on our ability to retain our President and Chief Executive Officer and to attract, retain and motivate qualified personnel.

We are highly dependent on Dr. Jeffrey M. Jonas, our Chief Executive Officer, President, and Director. We have entered into an employment agreement with Dr. Jonas, but he may terminate his employment with us at any time. Although we do not have any reason to believe that we will lose the services of Dr. Jonas in the foreseeable future, the loss of his services might impede the achievement of our research, development and commercialization objectives. We do not have any key-man life insurance on Dr. Jonas. We rely on consultants and advisors, including scientific, clinical and regulatory advisors, to assist us in formulating and implementing our development and commercialization strategy. 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, and may not be subject to our standard non-compete agreements. Recruiting and retaining qualified personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

Our employees may engage in misconduct or other improper activities, including violating applicable regulatory standards and requirements or engaging in insider trading, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to: comply with the regulations of the FDA and applicable non-U.S. regulators; provide accurate information to the FDA and applicable non-U.S. regulators; comply with healthcare fraud and abuse and anti-kick-back laws and regulations, in the U.S. and abroad; comply with anti-bribery and anti-corruption laws and regulations in the U.S. and abroad; report financial information or data accurately; or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials or other material information, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a code of conduct, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We face potential product liability exposure, and, if claims are brought against us, we may incur substantial liability.

The use of our product candidates in clinical trials and the sale of our products, if approved, expose us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others selling or otherwise

coming into contact with our product candidates. For example, we may be sued if any product candidate we study or product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical trials, 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, including as a result of interactions with alcohol or other drugs, knowledge of risks, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of patients from our clinical trials, or difficulty in enrolling clinical trials;
- substantial monetary awards to patients or other claimants;
- decreased demand for our products following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- increased FDA warnings on product labels;
- litigation costs;
- distraction of management's attention from our primary business;
- loss of revenue; and
- the inability to successfully gain approval and commercialize our product candidates or any future product candidates, if approved.

We maintain product liability insurance coverage for our clinical trials with a $10 million annual aggregate coverage limit. Nevertheless, our insurance coverage may be insufficient to reimburse us for any expenses or losses we may suffer. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. If and when we obtain marketing approval for our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may not be able to obtain this product liability insurance on commercially reasonable terms. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our stock price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, business and prospects could be materially adversely affected.

We will continue to incur significant costs as a result of operating as a public company, and our management team is required to devote substantial time to compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002 and rules subsequently implemented by the Securities and Exchange Commission and The NASDAQ Stock Market have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations cause us to incur significant legal and financial compliance costs, and make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. We conduct a process each year to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we dedicate internal resources, engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitation.

As of December 31, 2016, we had federal and state net operating loss carryforwards of $235.4 million and $234.3 million, respectively, which begin to expire in 2031. As of December 31, 2016, we also had federal and state research and development tax

credit carryforwards of $4.1 million and $1.6 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2016, we had federal orphan drug tax credit carryforwards of $29.8 million, which begin to expire in 2034. Under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, changes in our ownership may limit the amount of our net operating loss carryforwards and tax credit 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 research and development tax credit carryforwards before they expire. The completion of follow-on public offerings in April 2015, January 2016, September 2016 and our initial public offering, or IPO, together with private placements and other transactions that have occurred since our inception, may have triggered such an ownership change pursuant to Section 382. Any such limitation, whether as the result of our IPO, follow-on offerings, prior private placements, sales of our common stock by our existing stockholders or additional sales of our common stock by us, 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.

Unfavorable U.S. or 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 U.S. and global economy and financial markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including, weakened demand for our products, if any, 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 products if we receive marketing approval. 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 contract manufacturers, 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 development programs.

Despite the implementation of security measures, our internal computer systems and those of our third-party CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such system failure, accident, or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for our product candidates could result in delays in our regulatory submission and 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 guarantee that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

Risks Related to Our Financial Position and Need for Capital

We are a biopharmaceutical company with a limited operating history, and have not generated any revenue from product sales. We have incurred significant operating losses since our inception, and anticipate that we will incur continued losses for the foreseeable future.

We are a biopharmaceutical company with a limited operating history on which investors can base an investment decision. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We were incorporated in April 2010. Our operations to date have been limited primarily to organizing and staffing our company, raising capital and conducting research and development activities and clinical trials of our product candidates. We have never generated any revenue from product sales. We have not obtained regulatory approvals for any of our product candidates.

We have funded our operations to date through proceeds from sales of common stock, redeemable convertible preferred stock and, to a lesser extent, the issuance of convertible notes.

- On July 23, 2014, we completed the sale of 5,750,000 shares of our common stock in our IPO, at a price to the public of $18.00 per share, resulting in net proceeds of $94.0 million after deducting underwriting discounts and commissions and offering costs paid by us.
- On April 20, 2015, we completed the sale of 2,628,571 shares of our common stock in a public offering, at a price to the public of $52.50 per share, resulting in net proceeds of $129.1 million after deducting underwriting discounts and commissions and offering costs paid by us.
- On January 12, 2016, we completed the sale of 3,157,894 shares of our common stock in a public offering at a price to the public of $47.50 per share, resulting in net proceeds of $140.4 million after deducting underwriting discounts and commissions and offering costs paid by us.
- On September 14, 2016, we completed the sale of 5,062,892 shares of our common stock in a public offering at a price to the public of $39.75 per share, resulting in net proceeds of $189.2 million after deducting underwriting discounts and commissions and offering costs paid by us.

From our inception through December 31, 2016, we had received net proceeds of $643.3 million from such transactions. As of December 31, 2016, our cash, cash equivalents and marketable securities were $397.5 million. We have incurred significant net losses in each year since our inception, including net losses of $159.0 million for the year ended December 31, 2016 and $94.5 million for the year ended December 31, 2015. 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 clinical trials of our product candidates and efforts to seek regulatory approval for any product candidates that successfully complete clinical development. We also expect our general and administrative costs to increase as we expand our operations, including in anticipation of potential future commercialization efforts. In addition, if we obtain marketing approval for our product candidates, we will incur significant sales, marketing and outsourced-manufacturing expenses. As a public company, we incur additional legal and accounting 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 revenue. To date, we have not generated any revenue from our product candidates, and we do not know when, or if, we will generate any revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval of, and begin to sell a product. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- initiate and successfully complete all efficacy and safety clinical trials and non-clinical studies required to file for, and obtain, U.S. and foreign marketing approval for our product candidates;
- commercialize our product candidates, if approved, by developing a sales force or entering into collaborations with third parties; and
- achieve market acceptance of our product candidates in the medical community and with third-party payors.

Absent our entering into a collaboration or partnership agreement, we expect to incur significant sales and marketing costs as we prepare to commercialize our product candidates, if and when approved. Even if we successfully complete clinical development of our

product candidates, and our product candidates are approved for commercial sale, and despite expending these costs, our 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.

We will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently advancing our product candidates through non-clinical and clinical development, and preparing for a potential commercial launch if our product candidates are successfully developed and approved. Developing small molecule products and preparing for a potential launch are expensive, and we expect our research and development and general and administrative expenses to increase substantially in connection with our ongoing activities, particularly as we continue to advance our product candidates in clinical trials and if we generate positive data in our clinical programs. Depending on the status of regulatory approval or, if approved, commercialization of our product candidates, as well as the progress we make in selling our products, if approved, we will also require additional capital to fund operating needs. We may also need to raise additional funds if we choose to pursue additional indications and/or geographies for our product candidates, identify new potential opportunities or otherwise expand our activities more rapidly than we presently anticipate.

As of December 31, 2016, our cash, cash equivalents and marketable securities were $397.5 million. Based on our current operating plans, we expect that our existing cash, cash equivalents and marketable securities will be sufficient to fund our anticipated level of operations into the second quarter of 2018. Our current operating plan does not contemplate other development activities we may pursue or that all of the currently planned activities will proceed at the same pace, or that all of the activities will be fully initiated or completed during that time. We may use available capital resources sooner than we expect under our current operating plan. In addition, our operating plan may change. We may need or choose to seek additional funds sooner than planned, through public 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. In any event, we expect to require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. 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 in light of specific strategic considerations.

Any additional fundraising efforts may 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 or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may 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 candidates 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, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product, if approved, or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

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

We may seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, the ownership interest of our stockholders in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect the 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.

Risks Related to Our Common Stock

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

The market price for our common stock, similar to that of other biopharmaceutical companies, is 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, timing of, changes to, delays in or results from, non-clinical studies and clinical trials of our product candidates, including any adverse events, delays or announcements related to such studies or trials;
- any delay in filing for regulatory approval of our product candidates;
- the failure or delay of the FDA or any other regulatory authority to approve our product candidates, or any unexpected limitation on the approved indication or onerous condition of approval;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of our CNS therapies;
- regulatory or legal developments in the U.S. and other countries;
- adverse developments with respect to our intellectual property portfolio or failure to obtain or loss of exclusivity;
- 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;
- changes in healthcare laws affecting pricing, reimbursement or access;
- 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.

Our executive officers, directors, principal stockholders and their affiliates will continue to exercise significant control over our company, which will limit the ability of our stockholders to influence corporate matters and could delay or prevent a change in corporate control.

As of December 31, 2016, our executive officers, directors and principal stockholders, if they act together, given their existing holdings, will be able to influence significantly our management and affairs and the outcome of matters submitted to our stockholders for approval, including the election of directors and any sale, merger, consolidation, or sale of all or substantially all of our assets. Some of these stockholders acquired some or all of their shares of common stock for substantially less than the price of the shares of common stock acquired in our IPO or any follow-on offering, and these stockholders may have interests, with respect to their common stock, that are different from those of investors in our IPO or any follow-on offering and the concentration of voting power among these stockholders may have an adverse effect on the price of our common stock. In addition, this concentration of ownership might adversely affect the market price of our common stock by:

- delaying, deferring or preventing a change of control of us;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

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

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

We have broad discretion in how we use the proceeds from our follow-on public offerings, and may not use these proceeds effectively, which could affect our results of operations and cause our stock price to decline.

We have considerable discretion in the application of the net proceeds from our follow-on public offerings. We may use the net proceeds for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds from the follow-on offerings in a manner that does not produce income or that loses value.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, even one that may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may delay or prevent an acquisition of us or a change in our management. These provisions include a classified board of directors, a prohibition on actions by written consent of our stockholders and the ability of our board of directors to issue preferred stock without stockholder approval. In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively provide for an opportunity to obtain greater value for stockholders by requiring potential acquirers to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

We do not intend to pay dividends on our common stock and, consequently, the ability of our stockholders 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 an investor purchased them.

If equity research analysts stop publishing 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.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters are located in Cambridge, Massachusetts, and consist of 22,067 square feet in a multi-tenant building under a lease that will expire on February 28, 2022. In May 2016, we entered into a separate lease under which, beginning on September 1, 2016, we rent 19,805 square feet of additional office space in a separate multi-tenant building. The lease for the additional space will also expire in February 2022. We expect to lease additional space prior to the expiration of our leases to meet the needs of the business.

Item 3. Legal Proceedings

We are not a party to any legal proceedings, and we are not aware of any claims or actions pending or threatened against us. In the future, we might from time to time become involved in litigation relating to claims arising from our ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our financial position, results of operations or cash flows.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

On July 18, 2014, our common stock began trading on the NASDAQ Global Market under the symbol "SAGE". Prior to that time, there was no public market for our common stock. Shares sold in our initial public offering on July 17, 2014 were priced at $18.00 per share.

On February 15, 2017, the closing price for our common stock as reported on the NASDAQ Global Market was $57.58. The following table sets forth the high and low sales prices per share of our common stock as reported on the NASDAQ Global Market for the period indicated.

	Year Ended December 31,			
	2016		2015	
	High	Low	High	Low
First Quarter	$ 58.22	$ 26.28	$ 55.01	$ 35.00
Second Quarter	$ 39.99	$ 26.55	$ 89.04	$ 45.50
Third Quarter	$ 49.89	$ 29.81	$ 77.48	$ 39.98
Fourth Quarter	$ 56.45	$ 38.30	$ 62.64	$ 38.85

Stockholders

As of February 16, 2017, there were 9 stockholders of record of our common stock. The actual number of holders of our common stock is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers or held by other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Performance Graph

The following graph illustrates a comparison of the total cumulative stockholder return for our common stock since July 18, 2014, which is the date our shares began trading, through December 31, 2016, to two indices: the NASDAQ Composite Index and the NASDAQ Biotechnology Index. The graph assumes an initial investment of $100 on July 18, 2014, in our common stock, the stocks comprising the NASDAQ Composite Index, and the stocks comprising the NASDAQ Biotechnology Index. Historical stockholder return is not necessarily indicative of the performance to be expected for any future periods.

Comparison of Cumulative Total Return*
Among Sage Therapeutics, Inc., the NASDAQ Composite Index and the NASDAQ Biotechnology Index

* $100 invested on July 18, 2014 in stock or index.

The performance graph shall not be deemed to be incorporated by reference by means of any general statement incorporating by reference this Form 10-K into any filing under the Securities Act of 1933, as amended or the Securities Exchange Act of 1934, as amended, except to the extent that we specifically incorporate such information by reference, and shall not otherwise be deemed filed under such acts.

Dividend Policy

We have never paid or declared any cash dividends on our common stock, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. Any future determination to pay dividends will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law and other factors our board of directors deems relevant.

Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12. of Part III of this Annual Report.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report.

Item 6. Selected Consolidated Financial Data

The selected consolidated financial data set forth below are derived from our audited consolidated financial statements and may not be indicative of future operating results. The following selected consolidated financial data should be read in conjunction with Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the consolidated financial statements and the notes thereto included elsewhere in this Annual Report. The consolidated selected financial data in this section are not intended to replace our consolidated financial statements and the related notes included elsewhere in this Annual Report. Our historical results are not necessarily indicative of our future results.

	Year Ended December 31,				
	2016	2015	2014	2013	2012
	(in thousands, except for per share and per share data)				
Consolidated statements of operations data:					
Operating expenses:					
Research and development	$ 120,756	$ 69,357	$ 24,100	$ 14,357	$ 7,229
General and administrative	39,407	25,293	9,710	3,922	2,402
Total operating expenses	160,163	94,650	33,810	18,279	9,631
Loss from operations	(160,163)	(94,650)	(33,810)	(18,279)	(9,631)
Interest income, net	1,211	178	8	1	—
Other expense, net	(35)	(23)	(9)	(3)	(1)
Net loss	(158,987)	(94,495)	(33,811)	(18,281)	(9,632)
Accretion of redeemable convertible preferred stock to redemption value	—	—	(2,294)	(7)	(4)
Net loss attributable to common stockholders	$ (158,987)	$ (94,495)	$ (36,105)	$ (18,288)	$ (9,636)
Net loss per share attributable to common stockholders—basic and diluted(1)	$ (4.75)	$ (3.40)	$ (1.67)	$ (12.26)	$ (8.62)
Weighted average number of common shares used in net loss per share attributable to common stockholders—basic and diluted(1)	33,492,795	27,778,288	21,574,347	1,492,288	1,118,288

	Year Ended December 31,				
	2016	2015	2014	2013	2012
			(in thousands)		
Consolidated balance sheet data:					
Cash and cash equivalents	$ 168,517	$ 186,753	$ 127,766	$ 8,066	$ 2,802
Marketable securities	228,962	—	—	—	—
Working capital(2)	367,410	173,184	121,065	6,092	1,407
Total assets	404,531	189,016	129,665	8,532	2,995
Redeemable convertible preferred stock	—	—	—	37,709	14,970
Common stock and additional paid-in capital	688,963	335,035	188,730	139	—
Total stockholders' equity (deficit)	368,517	173,695	121,885	(31,536)	(13,394)

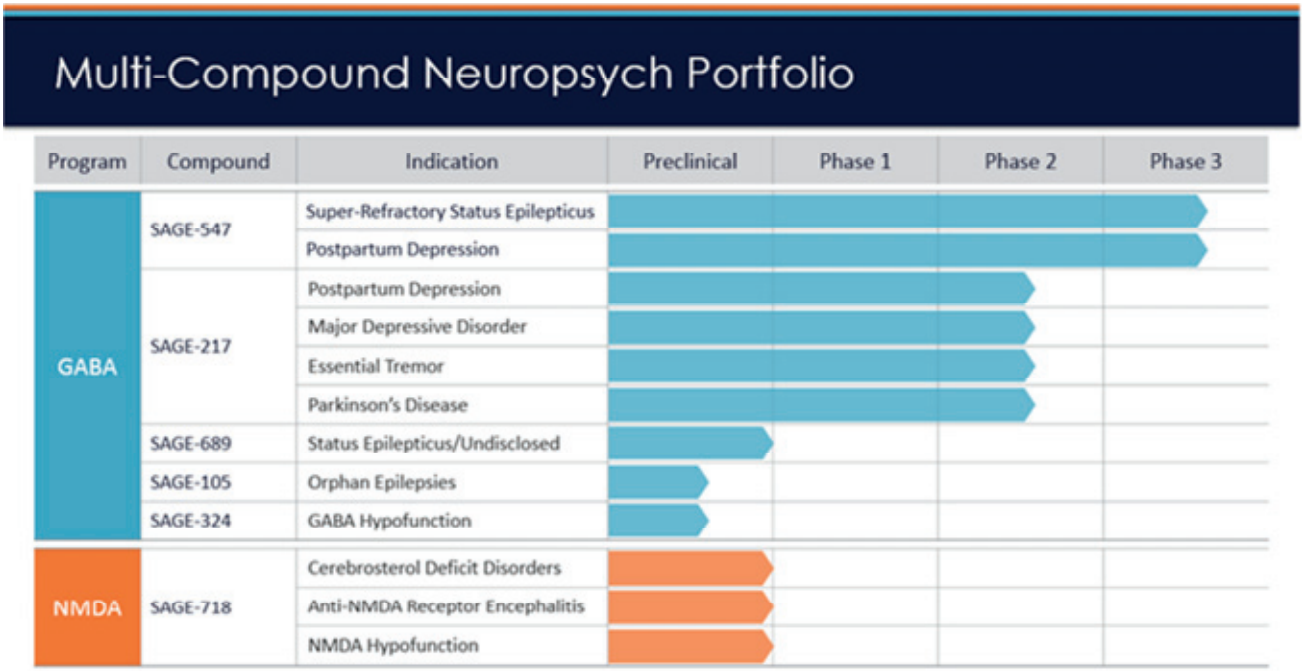
(1) See Note 9 to our consolidated financial statements appearing elsewhere in this Annual Report for further details on the calculation of basic and diluted net loss per share attributable to common stockholders.

(2) We define working capital as current assets less current liabilities.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operation

We are a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat life-altering central nervous system, or CNS, disorders, where there are no approved therapies or existing therapies are inadequate. We have a portfolio of product candidates with a current focus on modulating two critical CNS receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of $GABA_A$ receptors. The NMDA-type receptors of the glutamate receptor system are a major excitatory receptor system in the CNS. Dysfunction in these systems is implicated in a broad range of CNS disorders. We are targeting CNS indications where patient populations are easily identified, clinical endpoints are well-defined, and development pathways are feasible.

The following table summarizes the status of our development programs as of the date of this Annual Report.



Our lead product candidate, SAGE-547 (brexanolone USAN), is a proprietary intravenous, or IV, formulation of allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors, including both synaptic and extrasynaptic populations. We are currently conducting Phase 3 clinical trials of SAGE-547 in both super-refractory status epilepticus, or SRSE, and post-partum depression, or PPD.

Our Phase 3 clinical trial in SRSE, known as the STATUS Trial, is evaluating SAGE-547 as a potential adjunctive therapy in the treatment of SRSE. SRSE is a rare and life-altering condition in which a patient experiences a state of continuous seizure called status epilepticus, or SE, that continues or recurs despite standard treatment regimens normally sufficient to stop the seizure activity. We expect to report top-line results from the STATUS Trial in the first half of 2017. If successful, we believe the results from this Phase 3 clinical trial, together with other data from the SAGE-547 development program will be sufficient to form the basis of a New Drug Application, or NDA, submission to the FDA seeking approval for SAGE-547 in SRSE in the U.S. Based on scientific advice we received in the fourth quarter of 2016 from the European Medicines Agency, or EMA, we also believe our current Phase 3 clinical program in SRSE, if successful, will be sufficient to support a marketing authorization application, or MAA, to the EMA seeking approval of SAGE-547 for SRSE in the European Union, or EU.

Our Phase 3 clinical program in PPD is evaluating SAGE-547 as a potential treatment for PPD. PPD is a distinct and readily identified major depressive disorder that is a biological complication of childbirth, affecting a subset of women typically commencing in the third trimester of pregnancy or within four weeks after giving birth. We anticipate announcing top-line data from the Phase 3 clinical program, known as the Hummingbird Study, encompassing two placebo-controlled trials, in the second half of 2017. In the third quarter of 2016, we received Breakthrough Therapy designation from the FDA for SAGE-547 as a potential treatment for PPD. Based on input we received from the FDA during a Breakthrough Therapy meeting in the fourth quarter of 2016, we believe that, if successful, the results of the Phase 3 clinical program, together with the results of prior clinical studies of SAGE-547 in PPD, and

ongoing non-clinical studies, will be sufficient to support the submission of an NDA to the FDA seeking approval for SAGE-547 in PPD. In the fourth quarter of 2016, we also received **PRI**ority **ME**dicines (PRIME) designation from the EMA for SAGE-547 in the treatment of PPD.

Our most advanced next-generation product candidate is SAGE-217, a novel neuroactive steroid that, like SAGE-547, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. In the fourth quarter of 2016, we initiated our Phase 2 clinical program for SAGE-217 with a focus on four indications: two movement disorder indications, essential tremor and Parkinson's disease, and two mood disorder indications, major depressive disorder, or MDD, and PPD. In February 2017, we announced top-line results from the open-label, proof-of-concept portion (Part A) of our Phase 2 clinical trial of SAGE-217 in MDD which met our criteria for advancing SAGE-217 into the blinded, placebo-controlled portion of the Phase 2 MDD clinical trial (Part B). We expect to initiate Part B in the second quarter of 2017. We are also currently conducting the Phase 2 clinical trials of SAGE-217 in PPD, essential tremor and Parkinson's disease. We expect to report top-line results from the open-label portion of the Phase 2 clinical trial of SAGE-217 in Parkinson's disease in the first half of 2017. We anticipate reporting top-line results from the blinded, placebo-controlled Phase 2 clinical trials of SAGE-217 in essential tremor and PPD in the second half of 2017. We also have a portfolio of other novel compounds that target the $GABA_A$ receptors, including SAGE-105, SAGE-324 and SAGE-689, which are at earlier stages of development with a focus on both acute and chronic CNS disorders.

Our second area of focus is the development of novel compounds that target the NMDA receptor. The first product candidate selected for development from this program is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor. Our initial areas of focus for development of SAGE-718 will be cerebrosterol deficit disorders, Anti-NMDA Receptor Encephalitis, and other indications involving NMDA receptor hypofunction. We believe measuring levels of anti-NMDA receptor antibodies or decreased levels of cerebrosterol, a naturally occurring oxysterol, may represent biomarkers to identify, for future study, broader patient populations characterized by cognitive dysfunction and neuropsychiatric symptoms resulting from NMDA receptor dysfunction or hypofunction. Examples of these potential areas for future evaluation include certain types, aspects or subpopulations of a number of diseases such as depression, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, Huntington's disease, and neuropathic pain. We have completed Investigational New Drug, or IND-enabling non-clinical studies of SAGE-718, and plan to commence the Phase 1 clinical program in the first half of 2017.

We expect to continue our focus on allosteric modulation of the $GABA_A$ and NMDA receptor systems in the brain. The $GABA_A$ and NMDA receptor systems are broadly accepted as impacting many psychiatric and neurological disorders, spanning disorders of mood, seizure, cognition, anxiety, sleep, pain, epilepsy, and movement disorders, among others. We believe that we will have the opportunity to develop molecules from our internal portfolio with the goal of addressing a number of these disorders in the future. Our ability to identify and develop such novel CNS therapies is enabled by our proprietary chemistry platform that is centered, as a starting point, on knowledge of the chemical scaffolds of certain endogenous neuroactive steroids. We believe our knowledge of the chemistry and activity of allosteric modulators allows us to efficiently design molecules with different characteristics. This diversity enables us to regulate important properties such as half-life, brain penetration and receptor pharmacology to develop product candidates that have the potential for better selectivity, increased tolerability, and fewer off-target side effects than either current CNS therapies or previous therapies which have failed in development.

We have not generated any revenue to date. We have incurred net losses in each year since our inception, and we have an accumulated deficit of $320.3 million as of December 31, 2016. Our net losses were $159.0 million, $94.5 million and $33.8 million for the years ended December 31, 2016, 2015 and 2014, respectively. These losses have resulted principally from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to incur significant expenses and increasing operating losses for the foreseeable future.

We expect that our expenses will increase substantially in connection with our ongoing activities, as we:

- complete the ongoing Phase 3 clinical trials for SAGE-547 in SRSE and PPD, as well as additional clinical trials and non-clinical studies of SAGE-547 required for regulatory approval in SRSE and PPD;
- complete the ongoing and planned Phase 2 clinical trials of SAGE-217 in essential tremor, Parkinson's disease, PPD and MDD, and advance SAGE-217 further in development depending on the outcome of the ongoing trials;
- continue to advance SAGE-718, our early-stage novel allosteric modulator for NMDA, including planned commencement of a Phase 1 clinical program;
- continue non-clinical studies of SAGE-105 and SAGE-324with a focus on orphan epilepsies and indications involving GABA hypofunction;

- continue our research and development efforts to evaluate the potential for our other existing product candidates in the treatment of additional indications or in new formulations, and the identification of new drug candidates in the treatment of CNS disorders;
- advancing regulatory activities focused on a potential filing of an NDA and MAA for SAGE-547 in SRSE and an NDA in PPD;
- continue initial preparations for a potential future commercial launch;
- seek regulatory approvals for our product candidates that successfully complete clinical development;
- add personnel, including personnel to support our product development and future commercialization efforts, and incur increases in stock compensation expense related to existing and new personnel with respect to both service-based and performance-based awards;
- add operational, financial and management information systems; and
- maintain, leverage and expand our intellectual property portfolio.

As a result, in the future, we will need additional financing to support our continuing operations. Until such time that we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of public or debt financings or other sources, which may include collaborations with third parties. Arrangements with collaborators or others may require us to relinquish rights to certain of our technologies or product candidates. In addition, we may never successfully complete development of any of our product candidates; obtain adequate patent protection or other exclusivity for our product candidates; obtain necessary regulatory approval for our product candidates; or achieve commercial viability for any approved product. Adequate additional financing may not be available to us on acceptable terms, or at all. Our inability to raise capital as and when needed would have a negative impact on our financial condition and on our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2016 will enable us to fund our operating expenses and capital expenditure requirements, based on our current operating plan, into the second quarter of 2018. See "—Liquidity and Capital Resources".

Financial Operations Overview

Revenue

We have not generated any revenue from product sales since our inception, and do not expect to generate any revenue from the sale of products in the near future. If our developmental efforts result in clinical success and regulatory approval or collaboration agreements with third parties for our product candidates, we may generate revenue from those product candidates.

Operating Expenses

Our operating expenses since inception have consisted primarily of costs associated with research and development activities and general and administrative activities.

Research and Development Expenses

Research and development expenses, which consist primarily of costs associated with our product research and development efforts, are expensed as incurred. Research and development expenses consist primarily of:

- personnel costs, including salaries, benefits, stock-based compensation and travel expenses, for employees engaged in research and development functions;
- expenses incurred under agreements with contract research organizations, or CROs, and sites that conduct our non-clinical studies and clinical trials;
- expenses associated with manufacturing materials for use in clinical trials and developing external manufacturing capabilities;
- costs of outside consultants engaged in research and development activities, including their fees, stock-based compensation and travel expenses;

- other expenses related to our non-clinical studies and clinical trials and expenses related to our regulatory activities; and
- payments made under our third-party license agreements.

Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors and our clinical sites.

We have been developing our product candidates and focusing on other research and development programs, including exploratory efforts to identify new compounds, target validation for identified compounds and lead optimization for our earlier-validated programs. Our direct research and development expenses are tracked on a program-by-program basis, and consist primarily of external costs, such as fees paid to investigators, central laboratories, CROs and contract manufacturing organizations, or CMOs, in connection with our non-clinical studies and clinical trials; third-party license fees related to our product candidates; and fees paid to outside consultants who perform work on our programs. We do not allocate employee-related costs and other indirect costs to specific research and development programs because these costs are deployed across multiple product programs under research and development and, as such, are separately classified as unallocated research and development expenses.

Research and development activities are central to our business. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase in the foreseeable future as we continue or initiate clinical trials and non-clinical studies for certain product candidates, and pursue later stages of clinical development of our product candidates.

We cannot determine with certainty the duration and costs of the current or future clinical trials of our product candidates or if, when, or to what extent we will generate revenue from the commercialization and sale of any of our product candidates, if approved for marketing and sale. The duration, costs, and timing of clinical trials and development of our product candidates will depend on a variety of factors, including:

- the scope, size, rate of progress, and expense of our ongoing as well as any additional clinical trials, non-clinical studies, and other research and development activities;
- future clinical trial and non-clinical study results;
- decisions by regulatory authorities related to our product candidates;
- uncertainties in clinical trial enrollment rate or design;
- significant and changing government regulation; and
- the receipt and timing of any regulatory approvals, if any.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in enrollment in any of our clinical trials or need to enroll additional patients, we could be required to expend significant additional financial resources and time on the completion of clinical development.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel costs, consisting of salaries, benefits, stock-based compensation and travel expenses of our executive, finance, business, commercial, corporate development and other administrative functions. General and administrative expenses also include expenses incurred under agreements with third parties relating to evaluation, planning and preparation for a potential commercial launch; facilities and other related expenses, including rent, depreciation, maintenance of facilities, insurance and supplies; and professional fees for audit, tax and legal services, including legal expenses to pursue patent protection of our intellectual property.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support the expected growth in our business and the potential commercialization of our product candidates. We also anticipate increased expenses associated with general operations, including costs related to audit, tax and legal services, director and officer insurance premiums, and investor relations costs. Additionally, we anticipate an increase in payroll and related expenses as we continue to build our organizational capabilities, expand our operations, and prepare for possible future commercial operations, including sales and marketing of our product candidates, if approved.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that the estimates and assumptions involved in the accounting policies described below may have the greatest potential impact on our consolidated financial statements and, therefore, consider these to be our critical accounting policies. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions and conditions. While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel and vendors to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with performing research and development services on our behalf;
- other providers in connection with clinical trials;
- vendors in connection with non-clinical development activities; and
- vendors related to product manufacturing, development and distribution of clinical supplies.

We base our expenses related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical trials on our behalf. The financial terms of these agreements vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. When determining accruals, we estimate the time period over which services will be performed, enrollment of patients, number of sites activated and level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting expenses that are too high or too low in any particular period. To date, we have not made any material adjustments to our prior estimates of accrued research and development expenses.

Stock-Based Compensation

We recognize compensation expense for stock-based awards made to employees and non-employee directors, including grants of stock options and restricted stock, based on the estimated fair value on date of grant, over the requisite service period. For awards that vest upon achievement of a performance condition, we recognize compensation expense when achievement of the performance condition is met or during the period from which meeting the condition is deemed probable until the expected date of meeting the performance condition.

We have historically granted stock options with exercise prices equivalent to the fair value of our common stock as of the date of grant.

We measure stock-based awards granted to non-employee consultants at the fair value of the award on each date on which the awards vest. Compensation expense is recognized over the period during which services are rendered by such non-employee consultants until completed. At the end of each financial reporting period prior to the completion of the service, the fair value of these awards is re-measured using, for options, the then-current fair value of our common stock and updated assumptions in the Black-Scholes option-pricing model and using, for restricted stock, the then-current fair value of our common stock.

The fair value of each stock option grant is estimated using the Black-Scholes option-pricing model. Until July 18, 2014, we were a private company and we lacked company-specific historical and implied volatility information. Considering this and the short history of being a public company, starting in 2016, we estimate our expected volatility using a weighted average of the historical volatility of our publicly traded peer companies and the volatility of our common stock, and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our traded stock price. The expected term of our options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options, while the expected term of our options granted to consultants and non-employees has been determined based on the contractual term of the options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. The expected dividend yield is based on the fact that we have never paid cash dividends and do not expect to pay any cash dividends in the foreseeable future.

The assumptions we used to determine the fair value of stock options granted to employees and non-employee directors are as follows, presented on a weighted average basis:

	Year Ended December 31,		
	2016	2015	2014
Expected dividend yield	0%	0%	0%
Expected volatility	80.15%	90.54%	98.86%
Risk-free interest rate	1.47%	1.59%	1.95%
Expected life of option	6.05 years	6.03 years	6.38 years

These assumptions represented our best estimates, but the estimates involve inherent uncertainties and the application of our judgment. As a result, if factors change and we use significantly different assumptions or estimates when valuing our stock options, our stock-based compensation expense could be materially different. We recognize compensation expense for only the portion of awards that are expected to vest. In developing a forfeiture rate estimate for pre-vesting forfeitures, we have considered our historical experience of actual forfeitures. If our future actual forfeiture rate is materially different from our estimate, our stock-based compensation expense could be significantly different from what we have recorded in the current period.

Stock-based compensation expense recognized during the years ended December 31, 2016, 2015 and 2014 was as follows:

	Year Ended December 31,		
	2016	2015	2014
		(in thousands)	
Research and development	$ 11,197	$ 5,924	$ 1,093
General and administrative	11,823	9,316	1,419
	$ 23,020	$ 15,240	$ 2,512

During the years ended December 31, 2016 and 2015, we recorded $0.2 million and $0.1 million, respectively, of stock-based compensation expense related to our Employee Stock Purchase Plan.

As of December 31, 2016, we had unrecognized stock-based compensation expense related to our unvested service-based stock option awards of $43.6 million, which is expected to be recognized over the remaining weighted average vesting period of 2.77 years.

In addition, we granted 245,872 stock options that are both outstanding and unvested that will vest upon the achievement of certain performance criteria in the future. Total unrecognized stock-based compensation expense related to those awards was $5.2 million at December 31, 2016.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is set forth in Note 2 to the consolidated financial statements included in this Annual Report on Form 10-K.

Results of Operations

Comparison of the Years Ended December 31, 2016 and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015:

	Year Ended December 31,		Increase (Decrease)
	2016	2015	
		(in thousands)	
Operating expenses:			
Research and development	$ 120,756	$ 69,357	$ 51,399
General and administrative	39,407	25,293	14,114
Total operating expenses	$ 160,163	$ 94,650	$ 65,513
Loss from operations	(160,163)	(94,650)	(65,513)
Interest income, net	1,211	178	1,033
Other expense, net	(35)	(23)	(12)
Net loss	$ (158,987)	$ (94,495)	$ (64,492)

Research and development expenses

	Year Ended December 31,		Increase (Decrease)
	2016	2015	
		(in thousands)	
SAGE-547	$ 54,363	$ 38,104	$ 16,259
SAGE-217	18,668	6,408	12,260
SAGE-689	1,667	3,051	(1,384)
SAGE-718	6,457	3,317	3,140
Other research and development programs	7,927	4,484	3,443
Unallocated expenses	31,674	13,993	17,681
Total research and development expenses	$ 120,756	$ 69,357	$ 51,399

Research and development expenses for the year ended December 31, 2016 were $120.8 million, compared to $69.4 million for the year ended December 31, 2015. The increase of $51.4 million was primarily due to the following:

- an increase of $16.3 million in expenses related to our SAGE-547 program, due to the continued advancement of the program in clinical development, including ongoing enrollment in the Phase 3 clinical trial in SRSE; completion of the Phase 2 clinical trial of SAGE-547 in PPD; commencement of the Phase 3 clinical trial of SAGE-547 in PPD; conduct of supporting clinical pharmacology studies; and an increase in chemistry, manufacturing and control (CMC) work in preparation for a potential filing for regulatory approval. Expenses related to payments to consultants and licensors upon achievement of certain clinical development milestones were $0.8 million and $2.7 million for the years ended December 31, 2016 and 2015, respectively;
- an increase of $12.3 million in expenses related to our SAGE-217 program due to the conduct of the Phase 1 clinical program; the initiation of Phase 2-enabling toxicology, formulation and manufacturing activities; and commencement of Phase 2 clinical trials;
- a decrease of $1.4 million in expenses related to our SAGE-689 program due to the delay in commencement of a Phase 1 clinical trial as a result of a request from the FDA for additional non-clinical study data;
- an increase of $3.1 million in expenses due to the progression of our SAGE-718 program to IND-enabling non-clinical development and CMC activities in preparation for IND filing;
- an increase of $3.4 million in expenses related to research and development programs and discovery efforts focused on identifying new clinical candidates and additional indications of interest, and on our back-up programs; and
- an increase of $17.7 million in unallocated expenses, mainly due to the hiring of additional full-time employees to support the growth in our operations, including an increase of $5.3 million of non-cash stock-based compensation expense and an increase of $10.9 million in other employee-related costs, mainly for salaries. The amount of non-cash stock-based compensation expense recorded to research and development expense related to the achievement of performance-based

vesting criteria was $2.3 million and $2.0 million for the years ended December 31, 2016 and 2015, respectively, an increase of $0.3 million.

General and administrative expenses

	Year Ended December 31,		Increase (Decrease)
	2016	2015	
		(in thousands)	
Personnel-related	$ 22,107	$ 14,927	$ 7,180
Professional fees	6,941	4,333	2,608
Commercial planning	5,268	3,076	2,192
Other	5,091	2,957	2,134
Total general and administrative expenses	$ 39,407	$ 25,293	$ 14,114

General and administrative expenses for the years ended December 31, 2016 and 2015 were $39.4 million and $25.3 million, respectively. The increase of $14.1 million was primarily due to the following:

- an increase of $7.2 million in personnel-related costs due to the effects of hiring additional full-time employees to support operations, finance, human resources, legal and early commercial planning activities. Non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $2.7 million for the years ended December 31, 2016 and 2015;
- an increase of $2.6 million in professional fees due to increased costs associated with expanding operations, including costs related to audit, legal, and tax-related services, as well as investor relations costs;
- an increase of $2.2 million in commercial planning due to preparations for a potential commercial launch; and
- an increase of $2.1 million in other due to increased costs associated with facilities, mainly due to the increase in the amount of rented square feet of office space to accommodate our increase in employees.

Interest income, net and Other expense, net

Interest income, net, and other expense, net, for the years ended December 31, 2016 and 2015 were $1.2 million and $0.2 million, respectively. The primary reason for the increase was the increase in interest income from the purchase of marketable securities during the year ended December 31, 2016.

Comparison of the Years Ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014:

	Year Ended December 31,		Increase (Decrease)
	2015	2014	
		(in thousands)	
Operating expenses:			
Research and development	$ 69,357	$ 24,100	$ 45,257
General and administrative	25,293	9,710	15,583
Total operating expenses	94,650	33,810	60,840
Loss from operations	(94,650)	(33,810)	(60,840)
Interest income, net	178	8	170
Other income, net	(23)	(9)	(14)
Net loss	$ (94,495)	$ (33,811)	$ (60,684)

Research and development expenses

	Year Ended December 31,		Increase (Decrease)
	2015	2014	
		(in thousands)	
SAGE-547	$ 38,104	$ 9,137	$ 28,967
SAGE-217	6,408	2,764	3,644
SAGE-689	3,051	3,058	(7)
SAGE-718	3,317	-	3,317
Other research and development programs	4,484	3,088	1,396
Unallocated expenses	13,993	6,053	7,940
Total research and development expenses	$ 69,357	$ 24,100	$ 45,257

Research and development expenses for the year ended December 31, 2015 were $69.4 million, compared to $24.1 million for the year ended December 31, 2014. The increase of $45.3 million was primarily due to the following:

- an increase of $29.0 million in expenses of our SAGE-547 program, due to the advancement of the program into clinical development, including the completion of the Phase 1/2 clinical trial, commencement of activities for our Phase 3 clinical trial, an increase in work related to CMC and toxicology. For the years ended December 31, 2015 and 2014, payments made to consultants and licensors in connection with the achievement of development milestones met by consultants and licensors were $2.7 million and $0.4 million, respectively;
- an increase of $3.6 million in expenses of our SAGE-217 program with advancement of the lead optimization program through IND-enabling non-clinical development activities (e.g., toxicology studies, process development, and drug substance manufacturing), filing of the IND and initiation of the Phase 1 clinical trial in October 2015;
- an increase of $3.3 million in expenses of our SAGE-718 program, which became a development program during the year ended December 31, 2015;
- an increase of $1.4 million in expenses of our other research and development programs and discovery efforts for our next clinical candidates and back-up programs; and
- an increase of $7.9 million in unallocated expenses, including an increase of $4.8 million of non-cash stock-based compensation expense, due to the hiring of additional full-time employees to support the growth in our activities. The amount of non-cash stock-based compensation expense recorded to research and development expense related to the achievement of performance-based vesting criteria was $2.0 million for the year ended December 31, 2015. No stock-based compensation expense related to the achievement of performance-based vesting criteria was recorded to research and development expense for the year ended December 31, 2014.

General and administrative expenses

	Year Ended December 31,		Increase (Decrease)
	2015	2014	
		(in thousands)	
Personnel-related	$ 14,927	$ 4,337	$ 10,590
Professional fees	4,333	2,881	1,452
Commercial planning	3,076	907	2,169
Other	2,957	1,585	1,372
Total general and administrative expenses	$ 25,293	$ 9,710	$ 15,583

General and administrative expenses for the years ended December 31, 2015 and 2014 were $25.3 million and $9.7 million, respectively. The increase of $15.6 million in general and administrative expenses was primarily due to a $10.6 million increase in personnel-related costs due to the effects of hiring additional full-time employees to support operations, finance, human resources, legal and early commercial planning activities, including an increase of $7.9 million in non-cash stock-based compensation expense. The amount of non-cash stock-based compensation includes amounts related to the achievement of the performance-based vesting criteria of $2.7 million for the year ended December 31, 2015. No stock-based compensation expense related to the achievement of performance-based vesting criteria was recorded to general and administrative expenses for the year ended December 31, 2014. The

increase of $1.5 million in professional fees was primarily due to increased costs associated with being a public company, including costs related to audit, legal, regulatory and tax-related services, as well as investor relations costs. The increase of $2.2 million in commercial planning was associated preparations for a potential commercial launch.

Interest income, net

Interest income, net, for the years ended December 31, 2015 and 2014 was $0.2 million and $8,000, respectively. The increase in interest income was primarily due to increased cash and cash equivalent balances due to our July 2014 and April 2015 public offerings of common stock.

Other expense, net

Other expense, net was insignificant for the years ended December 31, 2015 and 2014.

Liquidity and Capital Resources

Since our inception in April 2010, we have not generated any revenue, and have incurred recurring net losses. As of December 31, 2016, we had an accumulated deficit of $320.3 million. From our inception through December 31, 2016, we received net proceeds of $643.3 million from the sales of redeemable convertible preferred stock, the issuance of convertible notes and the proceeds from our IPO in July 2014 and follow-on offerings in April 2015, January 2016 and September 2016.

On January 12, 2016, we completed the sale of 3,157,894 shares of our common stock in an underwritten public offering at a price to the public of $47.50 per share, resulting in net proceeds of $140.4 million after deducting commissions and underwriting discounts and offering costs paid by us.

On September 14, 2016, we completed the sale of 5,062,892 shares of our common stock in an underwritten public offering at a price to the public of $39.75 per share, resulting in net proceeds of $189.2 million after deducting commissions and underwriting discounts and offering costs paid by us.

As of December 31, 2016, our primary sources of liquidity were our cash, cash equivalents and marketable securities, which totaled $397.5 million. We invest our cash in money market funds, U.S. government securities, corporate bonds and commercial paper, with the primary objectives to preserve principal, provide liquidity and maximize income without significantly increasing risk.

The following table summarizes the primary sources and uses of cash for the periods presented below:

	Year Ended December 31,		
	2016	2015	2014
		(in thousands)	
Net cash provided by (used in):			
Operating activities	$ (118,678)	$ (70,681)	$ (27,042)
Investing activities	(230,540)	(198)	(128)
Financing activities	330,982	129,866	146,870
Net increase (decrease) in cash and cash equivalents	$ (18,236)	$ 58,987	$ 119,700

Operating Activities

Cash used in operating activities for the year ended December 31, 2016 was $118.7 million as compared to $70.7 million for the year ended December 31, 2015. The increase of $48.0 million was primarily due to the following:

- An increase of $64.5 million in cash used related to our net loss, primarily due to increased research and development activities related to our lead programs in development and increased general and administrative expenses due to increased headcount to support our operations;
- Offset by an increase of $6.3 million in non-cash charges, primarily due to an increase in stock-based compensation expense due to increased hiring during the year, including $5.0 million of stock-based compensation expense related to the achievement of performance-based vesting criteria; and
- Offset by an increase of $10.2 million in cash provided by changes in our operating assets and liabilities, primarily due to the growth of the business and the timing of vendor invoicing and payments.

Cash used in operating activities for the fiscal year ended December 31, 2015 was $70.7 million, compared to $27.0 million for the fiscal year ended December 31, 2014. The increase of $43.7 million was primarily due to the following:

- An increase of $60.7 million in cash used related to our net loss, primarily due to increased research and development activities related to our lead programs in development and increased general and administrative expenses due to increased headcount to support our operations;
- An increase of $13.9 million in non-cash charges, primarily due to an increase in stock-based compensation expense due to increased hiring during the year, including $4.8 million of stock-based compensation expense recognized upon the achievement of a performance-based vesting criteria; and
- An increase of $3.1 million in cash provided by changes in our operating assets and liabilities, primarily due to the growth of the business and the timing of vendor invoicing and payments.

Investing Activities

During the years ended December 31, 2016 and 2015, net cash used by investing activities was $230.5 million and $0.2 million, respectively. During the year ended December 31, 2016, we used $259.1 million to purchase marketable securities and received proceeds of $30.5 million from sales of marketable securities.

During the years ended December 31, 2015 and 2014, we purchased no marketable securities; however, during the years ended December 31, 2015 and 2014, we used $0.2 million and $0.1 million, respectively, of cash for purchases of property and equipment.

Financing Activities

During the years ended December 31, 2016, 2015 and 2014, net cash provided by financing activities was $331.0 million, $129.9 million and $146.9 million, respectively.

- Net cash provided by financing activities in the year ended December 31, 2016 primarily consisted of $329.6 million of net proceeds from follow-on underwritten public offerings of our common stock after deducting commissions and underwriting discounts and offering costs.
- Net cash provided by financing activities in the year ended December 31, 2015 primarily consisted of $129.1 million of net proceeds from a follow-on underwritten public offering of our common stock after deducting commissions and underwriting discounts and offering costs.
- Net cash provided by financing activities in the year ended December 31, 2014 consisted primarily of $94.0 million in net proceeds from our IPO on July 23, 2014 and $52.9 million from the issuance of Series B and Series C redeemable convertible preferred stock.

Operating Capital Requirements

To date, we have not generated any revenue from product sales. We do not know when, or if, we will generate any revenue from product sales. We do not expect to generate significant revenue from product sales unless and until we successfully develop, obtain regulatory approval of and commercialize one of our current or future product candidates. We anticipate that we will continue to generate losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, continue preparations for potential future commercialization, and begin to commercialize any products, if approved. We expect to incur additional costs associated with general operations. In addition, subject to obtaining regulatory approval of any of our product candidates, we expect to incur significant commercialization expenses for product sales, marketing and outsourced manufacturing. Accordingly, we anticipate that we will need substantial additional funding in connection with our continuing operations.

Based on our current operating plans, we expect that our existing cash, cash equivalents and marketable securities as of December 31, 2016, will enable us to fund our operating expenses and capital expenditure requirements into the second quarter of 2018. During that time, we expect that our expenses will increase substantially as we:

- complete the ongoing Phase 3 clinical trials for SAGE-547 in SRSE and PPD, as well as additional clinical trials and non-clinical studies of SAGE-547 required for regulatory approval in SRSE and PPD;
- complete the ongoing and currently planned Phase 2 clinical trials of SAGE-217 in essential tremor, Parkinson's disease, PPD and MDD, and advance SAGE-217 further in development depending on the outcome of the ongoing trials;

- continue to advance SAGE-718, our early-stage novel allosteric modulator for NMDA, including planned commencement of a Phase 1 clinical program;
- continue non-clinical studies of SAGE-105 and SAGE-324with a focus on orphan epilepsies and indications involving GABA hypofunction;
- continue our research and development efforts to evaluate the potential for our other existing product candidates in the treatment of additional indications or in new formulations, and the identification of new drug candidates in the treatment of CNS disorders;
- advancing regulatory activities focused on a potential filing of an NDA and MAA for SAGE-547 in SRSE and an NDA in PPD;
- continue initial preparations for a potential future commercial launch;
- seek regulatory approvals for our product candidates that successfully complete clinical development;
- add personnel, including personnel to support our product development and future commercialization efforts, and incur increases in stock compensation expense related to existing and new personnel with respect to both service-based and performance-based awards;
- add operational, financial and management information systems; and
- maintain, leverage and expand our intellectual property portfolio.

Our current operating plan does not contemplate other development activities that we may pursue or that all of our currently planned activities will proceed at the same pace, or that all of these activities will be fully initiated or completed during that time. We have based our estimates on assumptions that could change, and we may use our available capital resources sooner than we currently expect. We may also choose to change or increase our development efforts. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to estimate the amounts of increased capital outlays and operating expenditures necessary to complete the development and commercialization of our product candidates.

Our future capital requirements will depend on many factors, including:

- the ability of our product candidates to progress through clinical development successfully;
- the initiation, progress, timing, costs, and results of non-clinical studies and clinical trials for our existing and future product candidates; the number and length of clinical trials required by regulatory authorities to support regulatory approval; and the costs of preparing regulatory filings;
- the cost, timing, and outcome of regulatory reviews and approvals;
- the level, timing and amount of costs associated with preparing for a potential future commercial launch in the near term, and if we are successful in obtaining regulatory approval of any of product candidates, the cost of executing a commercial launch of the approved product, including manufacturing-related costs;
- the number and characteristics of the product candidates we pursue and the nature and scope of our discovery and development programs;
- the scope and timing of potential expansion of our activities outside the U.S.;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the extent to which we acquire or in-license other products and technologies; and
- our ability to establish any future collaboration arrangements on favorable terms, if at all.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other sources of funding. 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 in light of specific strategic considerations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, 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 and may require the issuance of warrants, which could potentially dilute the ownership

interest of our stockholders. If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams or research programs or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations at December 31, 2016 and the effect such obligations are expected to have on our liquidity and cash flow in future periods:

	Payments Due by Period				
	Total	Less Than 1 year	1-3 Years	3-5 Years	More Than 5 years
			(in thousands)		
Operating lease commitments(1)	$ 14,314	$ 2,666	$ 5,500	$ 5,668	$ 480
Total(1)(2)(3)(4)	$ 14,314	$ 2,666	$ 5,500	$ 5,668	$ 480

Amounts related to contingent milestone payments are not considered contractual obligations as they are contingent on the successful achievement of certain milestones. These contingent milestones may not be achieved. We have not included any of these amounts in the table as we cannot estimate or predict when, or if, these amounts will become due.

(1) We lease 22,067 square feet of office space in Cambridge, Massachusetts, in a multi-tenant building under an operating lease that will expire in February 2022. In May 2016, we entered into a lease under which, beginning in September 2016, we rent 19,805 square feet of additional office space, also in Cambridge, Massachusetts, in a separate multi-tenant building. The lease for the additional space will expire in February 2022. The minimum lease payments in the table do not include related common area maintenance charges or real estate taxes, because those costs are variable.

(2) We have acquired exclusive and non-exclusive rights to use, research, develop and offer for sale certain products and patents under license agreements with Washington University, CyDex Pharmaceuticals, Inc. and two license agreements with The Regents of the University of California. The license agreements obligate us to make payments to the licensors for license fees, milestones, license maintenance fees and royalties. We are obligated to make future remaining milestone payments under these agreements of up to an aggregate of $33.4 million upon achieving certain milestones, related to clinical development, regulatory approvals and sales. For the year ended December 31, 2016, we recorded $0.8 million of research and development expense under these license agreements related to milestones.

(3) We enter into contracts in the normal course of business with CROs for clinical trials, non-clinical research studies and testing, manufacturing and other services and products as part of general operations. These contracts generally provide for termination upon notice, and we believe that our non-cancelable obligations under these agreements are not material.

(4) Under a January 2014 consulting agreement, we are obligated to make remaining milestone payments of up to $1.5 million and to issue up to 87,303 shares of our common stock to a nonemployee consultant upon achieving certain clinical development milestones and regulatory approval milestones. For the year ended December 31, 2016, we did not record any expense or make any milestone payments under this consulting agreement.

Off-Balance Sheet Arrangements

We do not currently have, nor did we have during the periods presented, any off-balance sheet arrangements as defined by SEC rules.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We had cash, cash equivalents and marketable securities of approximately $397.5 million as of December 31, 2016. The primary objectives of our investment activities are to preserve principal, provide liquidity and maximize income without significantly increasing risk. Our primary exposure to market risk relates to fluctuations in interest rates, which are affected by changes in the general level of U.S. interest rates. Given the short-term nature of our cash, cash equivalents and marketable securities, we believe that a sudden change in market interest rates would not be expected to have a material impact on our financial condition and/or results of operation. We do not have any foreign currency or other derivatives financial instruments.

We do not believe that our cash, cash equivalents and marketable securities have significant risk of default or illiquidity. While we believe our cash, cash equivalents and marketable securities do not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in market value. In addition, we maintain significant amounts of cash, cash equivalents and marketable securities at one or more financial institutions that are in excess of federally insured limits.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our results of operations during the year ended December 31, 2016.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report. An index of those financial statements is found in Item 15.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Securities Exchange Act of 1934 is (1) recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our President and Chief Executive Officer, who is our principal executive officer and Chief Financial Officer, who is also our principal financial and accounting officer, as appropriate, to allow timely decisions regarding required disclosure.

As of December 31, 2016, our management, with the participation of our principal executive officer and principal financial and accounting officer, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934). Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial and accounting officer have concluded based upon the evaluation described above that, as of December 31, 2016, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rule 13a—15(f) under the Exchange Act). Our internal control over financial reporting is a process designed under the supervision of our principal executive officer and principal financial officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of our financial statements for external purposes in accordance with generally accepted accounting principles. Management evaluated the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in *Internal Control—Integrated Framework* (the 2013 Framework). Management, under the supervision and with the participation of the principal executive officer and principal financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2016 and concluded that it was effective.

The effectiveness of our internal control over financial reporting as of December 31, 2016 has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report, which is included herein.

Changes in Internal Control over Financial Reporting

There were no changes to our internal control over financial reporting that occurred during the period covered by this Annual Report that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 11. Executive Compensation

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

Item 14. Principal Accounting Fees and Services

The information required by this Item is incorporated herein by reference to the information that will be contained in our proxy statement related to the 2017 Annual Meeting of Stockholders, which we intend to file with the Securities and Exchange Commission within 120 days of the end of our fiscal year pursuant to General Instruction G(3) of Form 10-K.

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are filed as part of this report:

(1) Financial Statements:

(2) Financial Statement Schedules:

All financial statement schedules have been omitted because they are not applicable, not required or the information required is shown in the financial statements or the notes thereto.

(3) Exhibits. The exhibits filed as part of this Annual Report on Form 10-K are set forth on the Exhibit Index immediately following our consolidated financial statements. The Exhibit Index is incorporated herein by reference.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

Pursuant to the requirements of the Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized.

SAGE THERAPEUTICS, INC.

Date: February 24, 2017

By: /s/ Jeffrey M. Jonas

Jeffrey M. Jonas, M.D.
Chief Executive Officer, President and Director
(Principal Executive Officer)

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed by the following persons in the capacities indicated below and on the dates indicated:

Signature	Title	Date
/s/ Jeffrey M. Jonas Jeffrey M. Jonas, M.D.	Chief Executive Officer, President and Director (Principal Executive Officer)	February 24, 2017
/s/ Kimi Iguchi Kimi Iguchi	Chief Financial Officer (Principal Financial and Accounting Officer)	February 24, 2017
/s/ Michael F. Cola Michael F. Cola	Director	February 24, 2017
/s/ Steven Paul Steven Paul, M.D.	Director	February 24, 2017
/s/ Kevin P. Starr Kevin P. Starr	Director	February 24, 2017
/s/ Howard Pien Howard Pien	Director	February 24, 2017
/s/ James Frates James Frates	Director	February 24, 2017
/s/ Geno Germano Geno Germano	Director	February 24, 2017

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of
Sage Therapeutics, Inc.

In our opinion, the accompanying consolidated balance sheets and the related consolidated statements of operations and comprehensive loss, of changes in redeemable convertible preferred stock and stockholders' equity (deficit) and of cash flows present fairly, in all material respects, the financial position of Sage Therapeutics, Inc. and its subsidiaries at December 31, 2016 and 2015, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2016 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2016, based on criteria established in *Internal Control—Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). The Company's management is responsible for these financial statements, for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on these financial statements and on the Company's internal control over financial reporting based on our audits (which were integrated audits in 2016 and 2015). We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audits of the financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
February 24, 2017

Sage Therapeutics, Inc. and Subsidiaries
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31, 2016	December 31, 2015
Assets		
Current assets:		
Cash and cash equivalents	$ 168,517	$ 186,753
Marketable securities	228,962	—
Prepaid expenses and other current assets	5,100	1,738
Total current assets	402,579	188,491
Property and equipment, net	1,388	286
Restricted cash	564	39
Deferred offering costs	—	200
Total assets	$ 404,531	$ 189,016
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 12,817	$ 5,159
Accrued expenses	22,352	10,148
Total current liabilities	35,169	15,307
Other liabilities	845	14
Total liabilities	36,014	15,321
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value per share; 5,000,000 shares authorized at December 31, 2016 and 2015; no shares issued or outstanding at December 31, 2016 and 2015	—	—
Common stock, $0.0001 par value per share; 120,000,000 shares authorized at December 31, 2016 and 2015; 37,222,518 and 28,823,549 shares issued at December 31, 2016 and 2015, respectively; 37,222,172 and 28,823,549 shares outstanding at December 31, 2016 and 2015, respectively	4	3
Treasury stock, at cost; 346 shares at December 31, 2016 and none at December 31, 2015	(17)	-
Additional paid-in capital	688,959	335,032
Accumulated deficit	(320,327)	(161,340)
Accumulated other comprehensive income (loss)	(102)	—
Total stockholders' equity	368,517	173,695
Total liabilities and stockholders' equity	$ 404,531	$ 189,016

The accompanying notes are an integral part of these consolidated financial statements.

Sage Therapeutics, Inc. and Subsidiaries
Consolidated Statements of Operations and Comprehensive Loss
(in thousands, except share and per share data)

	Year Ended December 31,		
	2016	2015	2014
Operating expenses:			
Research and development	$ 120,756	$ 69,357	$ 24,100
General and administrative	39,407	25,293	9,710
Total operating expenses	160,163	94,650	33,810
Loss from operations	(160,163)	(94,650)	(33,810)
Interest income, net	1,211	178	8
Other expense, net	(35)	(23)	(9)
Net loss	$ (158,987)	$ (94,495)	$ (33,811)
Accretion of redeemable convertible preferred stock to redemption value	—	—	(2,294)
Net loss attributable to common stockholders	$ (158,987)	$ (94,495)	$ (36,105)
Net loss per share attributable to common stockholders—basic and diluted	$ (4.75)	$ (3.40)	$ (1.67)
Weighted average number of common shares used in net loss per share attributable to common stockholders—basic and diluted	33,492,795	27,778,288	21,574,347
Comprehensive loss:			
Net loss	$ (158,987)	$ (94,495)	$ (33,811)
Other comprehensive items:			
Unrealized loss on marketable securities	(102)	—	—
Total other comprehensive loss	(102)	—	—
Total comprehensive loss	$ (159,089)	$ (94,495)	$ (33,811)

The accompanying notes are an integral part of these consolidated financial statements.

Sage Therapeutics, Inc. and Subsidiaries
Consolidated Statements of Changes in Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share data)

	Series A, B and C Redeemable Convertible Preferred Stock		Common Stock		Treasury Stock		Additional Paid-in Capital	Accumulated other comprehensive income (loss)	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount				
Balances at December 31, 2013	37,750,000	$ 37,709	1,622,761	$ -	—	$ -	$ 139	$ -	$ (31,675)	$ (31,536)
Issuance of Series B Preferred Stock, net of issuance costs of $30	9,999,999	14,970	—	—	—	—	—	—	—	—
Issuance of Series C Preferred Stock, net of issuance costs of $110	8,973,905	37,890	—	—	—	—	—	—	—	—
Issuance of common stock from exercise of stock options	—	—	87,475	—	—	—	40	—	—	40
Vesting of restricted stock	—	—	138,108	—	—	—	14	—	—	14
Issuance of common stock in payment of consultant fees	—	—	15,872	—	—	—	127	—	—	127
Stock-based compensation expense	—	—	—	—	—	—	2,512	—	—	2,512
Accretion of redeemable convertible preferred stock to redemption value	—	2,294	—	—	—	—	(935)	—	(1,359)	(2,294)
Conversion of redeemable convertible preferred stock to common stock	(56,723,904)	(92,863)	18,007,575	2	—	—	92,861	—	—	92,863
Initial public offering of common stock, net of offering costs	—	—	5,750,000	1	—	—	93,969	—	—	93,970
Net loss	—	—	—	—	—	—	—	—	(33,811)	(33,811)
Balances at December 31, 2014	—	—	25,621,791	3	—	—	188,727	—	(66,845)	121,885
Issuance of common stock from exercise of stock options	—	—	417,475	—	—	—	603	—	—	603
Vesting of restricted stock	—	—	128,051	—	—	—	17	—	—	17
Issuance of common stock under employee stock purchase plan	—	—	3,852	—	—	—	127	—	—	127
Issuance of common stock in payment of consultant fees	—	—	23,809	—	—	—	1,211	—	—	1,211
Stock-based compensation expense	—	—	—	—	—	—	15,176	—	—	15,176
Public offering of common stock, net of offering costs	—	—	2,628,571	—	—	—	129,171	—	—	129,171
Net loss	—	—	—	—	—	—	—	—	(94,495)	(94,495)
Balances at December 31, 2015	—	—	28,823,549	3	—	—	335,032	—	(161,340)	173,695
Issuance of common stock from exercise of stock options	—	—	124,557	—	—	—	1,011	—	—	1,011
Vesting of restricted stock	—	—	42,781	—	—	—	11	—	—	11

Sage Therapeutics, Inc. and Subsidiaries
Consolidated Statements of Changes in Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share data)

	Series A, B and C Redeemable Convertible Preferred Stock		Common Stock		Treasury Stock		Additional Paid-in Capital	Accumulated other comprehensive income (loss)	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount				
Issuance of common stock under employee stock purchase plan	—	—	10,499	—	—	—	510	—	—	510
Purchase of treasury stock	—	—	—	—	346	(17)	—	—	—	(17)
Stock-based compensation expense	—	—	—	—	—	—	22,855	—	—	22,855
Public offerings of common stock, net of offering costs	—	—	8,220,786	1	—	—	329,540	—	—	329,541
Unrealized loss on available-for-sale securities	—	—	—	—	—	—	—	(102)	—	(102)
Net loss	—	—	—	—	—	—	—	—	(158,987)	(158,987)
Balances at December 31, 2016	—	$ —	37,222,172	$ 4	346	$ (17)	$688,959	$ (102)	$ (320,327)	$ 368,517

The accompanying notes are an integral part of these consolidated financial statements.

Sage Therapeutics, Inc. and Subsidiaries
Consolidated Statements of Cash Flows
(in thousands)

	Year Ended December 31,		
	2016	2015	2014
Cash flows from operating activities			
Net loss	$ (158,987)	$ (94,495)	$ (33,811)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	23,020	15,240	2,512
Non-cash licensing and consulting fees	—	1,211	127
Premium on marketable securities	(756)	—	—
Amortization of premium on marketable securities	286	—	—
Depreciation	281	115	51
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(3,362)	(681)	(715)
Accounts payable	7,796	2,590	441
Accrued expenses and other liabilities	13,044	5,339	4,353
Net cash used in operating activities	(118,678)	(70,681)	(27,042)
Cash flows from investing activities			
Proceeds from sales and maturities of marketable securities	30,499	—	—
Purchases of marketable securities	(259,093)	—	—
Purchases of property and equipment	(1,421)	(198)	(128)
Increase in restricted cash	(525)	—	—
Net cash used in investing activities	(230,540)	(198)	(128)
Cash flows from financing activities			
Proceeds from the issuance of Series B preferred stock, net of issuance costs	-	-	14,970
Proceeds from the issuance of Series C preferred stock, net of issuance costs	-	-	37,890
Proceeds from stock option exercises and employee stock purchase plan issuances	1,406	730	40
Payments of offering costs	(599)	(584)	(2,285)
Proceeds from public offerings of common stock, net of commissions and underwriting discounts	330,175	129,720	96,255
Net cash provided by financing activities	330,982	129,866	146,870
Net increase (decrease) in cash and cash equivalents	(18,236)	58,987	119,700
Cash and cash equivalents at beginning of period	186,753	127,766	8,066
Cash and cash equivalents at end of period	$ 168,517	$ 186,753	$ 127,766
Supplemental disclosure of non-cash financing activities			
Accretion of redeemable convertible preferred stock to redemption value	$ —	$ —	$ 2,294
Conversion of preferred stock to common stock	$ —	$ —	$ 92,863
Purchases of property and equipment included in accounts payable	$ 8	$ —	$ —
Public offering costs included in accounts payable or accrued expenses	$ —	$ 165	$ —

The accompanying notes are an integral part of these consolidated financial statements.

1. Nature of the Business

Sage Therapeutics, Inc. ("Sage" or the "Company") is a clinical-stage biopharmaceutical company committed to developing and commercializing novel medicines to treat life-altering central nervous system, or CNS, disorders, where there are no approved therapies or existing therapies are inadequate. The Company has a portfolio of product candidates with a current focus on modulating two critical CNS receptor systems, GABA and NMDA. The GABA receptor family, which is recognized as the major inhibitory neurotransmitter in the CNS, mediates downstream neurologic and bodily function via activation of $GABA_A$ receptors. The NMDA-type receptors of the glutamate receptor system are a major excitatory receptor system in the CNS. Dysfunction in these systems is implicated in a broad range of CNS disorders. The Company is targeting CNS indications where patient populations are easily identified, clinical endpoints are well-defined, and development pathways are feasible.

The Company was incorporated under the laws of the State of Delaware on April 16, 2010, and commenced operations on January 19, 2011 as Sterogen Biopharma, Inc. On September 13, 2011, the Company changed its name to Sage Therapeutics, Inc. under its Second Amended and Restated Certificate of Incorporation.

The Company is subject to risks and uncertainties common to companies in the biotech industry, including, but not limited to, the risks associated with developing product candidates at each stage of non-clinical and clinical development; the challenges associated with gaining regulatory approval of such product candidates; the risks associated with commercializing pharmaceutical products, if it is able to obtain regulatory approval; the potential for development by third parties of new technological innovations that may compete with the Company's products; the dependence on key personnel; the challenges of protecting proprietary technology; the need to comply with government regulations; the high costs of drug development; and the uncertainty of being able to secure additional capital when needed to fund operations.

The Company has incurred losses and negative cash flows from operations since its inception. As of December 31, 2016, the Company had an accumulated deficit of $320.3 million. From its inception through December 31, 2016, the Company received net proceeds of $643.3 million from the sales of redeemable convertible preferred stock, the issuance of convertible notes, and the proceeds from its initial public offering ("IPO") in July 2014 and follow-on underwritten public offerings in April 2015, January 2016 and September 2016. Until such time, if ever, as the Company can generate substantial product revenue, the Company expects to finance its cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other sources of funding. If the Company is unable to raise additional funds through equity or debt financings when needed, the Company may be required to delay, limit, reduce or terminate product development or future commercialization efforts or grant rights to develop and market products or product candidates that the Company would otherwise prefer to develop and market itself.

Based on its current operating plans, the Company believes its cash, cash equivalents and marketable securities of $397.5 million as of December 31, 2016 will be sufficient to fund its anticipated level of operations and capital expenditures into the second quarter of 2018.

2. Summary of Significant Accounting Policies

The following is a summary of significant accounting policies followed in the preparation of these financial statements.

Basis of Presentation

The accompanying consolidated financial statements include those of the Company and its subsidiaries after elimination of all intercompany accounts and transactions. The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP").

Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of three months or less at the date of purchase to be cash equivalents.

Marketable securities

Marketable securities consist of investments with original maturities greater than ninety days. The Company considers its investment portfolio of investments to be available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are reported as a component of accumulated other comprehensive items in stockholders' equity. Realized gains and losses and declines in value judged to be other than temporary are included as a component of other expense, net, based on the specific identification method. When determining whether a decline in value is other than temporary, the Company considers various factors, including whether the Company has the intent to sell the security, and whether it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis. No declines in value were deemed to be other than temporary during the year ended December 31, 2016.

Restricted Cash

A deposit of $39,000 was restricted from withdrawal as of December 31, 2016 and 2015. The restriction is related to securing the Company's facility lease and expires in 2022 in accordance with the operating lease agreement. This balance is included in restricted cash on the accompanying consolidated balance sheets.

A deposit of $0.5 million was restricted from withdrawal as of December 31, 2016. The restriction is related to securing the facility lease in May 2016, under which the Company rented 19,805 square feet of additional office space in a separate multi-tenant building beginning in September 2016. The lease for the additional space will expire in February 2022. The restriction expires in 2022, in accordance with the operating lease agreement. This balance is included in restricted cash on the accompanying consolidated balance sheet.

Property and Equipment

Property and equipment are recorded at cost and depreciated over their estimated useful lives using the straight-line method. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is credited or charged to income. Repairs and maintenance costs are expensed as incurred.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in the use of the assets. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset over its fair value, determined based on discounted cash flows. To date, the Company has not recorded any impairment losses on long-lived assets.

Research and Development

Research and development expenses are comprised of costs incurred in performing research and development activities, including salaries and benefits, overhead costs, depreciation, contract services and other related costs. Research and development costs are expensed to operations as the related obligation is incurred.

Research Contract Costs and Accruals

The Company has entered into various research and development contracts with research institutions and other companies both inside and outside of the United States. These agreements are generally cancelable, and related payments are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Patent Costs

The Company expenses patent costs as incurred and classifies such costs as general and administrative expenses in the accompanying statements of operations and comprehensive loss.

Stock-Based Compensation

The Company recognizes compensation expense for stock-based awards made to employees and nonemployee directors, including grants of stock options and restricted stock, based on the estimated fair value on the date of grant, over the requisite service period.

For stock-based options and restricted stock issued to nonemployee consultants, the Company recognizes the fair value of the award as an expense over the period in which the related services are received. The fair value of the awards and measurement of related stock-based compensation is subject to periodic adjustments as the awards vest.

For awards that vest upon achievement of a performance condition, the Company recognizes compensation expense when achievement of the performance condition is deemed probable over the implicit service period.

The fair value of each option grant is estimated using the Black-Scholes option-pricing model. Through July 2014, the Company was a private company and lacked sufficient Company-specific historical and implied volatility information. Therefore, in 2016, the Company began estimating its expected volatility using a weighted average of the historical volatility of publicly traded peer companies and the volatility of its common stock, and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its traded stock price for the duration of the expected term. The expected term of the Company's options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options, while the expected term of its options granted to consultants and nonemployees has been determined based on the contractual term of the options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. The expected dividend yield is based on the fact that the Company never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

The Company also applies a forfeiture rate in order to calculate stock-based compensation expense. To the extent actual forfeitures differ from the estimates, the difference will be recorded as a cumulative adjustment in the period in which the estimates are revised. The Company recognizes stock-based compensation expense for only the portion of awards that are expected to vest. Expected forfeitures are based on the Company's historical experience and management's expectations of future forfeitures.

Treasury Stock

The Company records treasury stock at cost. Treasury stock includes shares received from an employee as consideration for an exercise of stock options.

Basic and Diluted Net Loss Per Share

Upon the closing of the Company's IPO in July 2014, all of the Company's outstanding shares of redeemable convertible preferred stock were converted into shares of common stock. Prior to this conversion, the Company followed the two-class method when computing net loss per share as the Company had issued shares that meet the definition of participating securities. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. The Company's redeemable convertible preferred shares contractually entitled the holders of such shares to participate in dividends, but did not contractually require the holders of such shares to participate in losses of the Company. Accordingly, the two-class method did not apply for periods in which the Company reported a net loss or a net loss attributable to common stockholders resulting from dividends or accretion related to its redeemable convertible preferred shares.

Basic net loss per share attributable to common stockholders is computed by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net loss per share attributable to common stockholders is computed by dividing the diluted net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of outstanding stock options and unvested restricted common shares, as determined using the treasury stock method. For periods in which the Company has reported net losses, diluted net loss per common share attributable to common stockholders is the same as

basic net loss per common share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is antidilutive.

The Company reported a net loss attributable to common stockholders for the years ended December 31, 2016, 2015 and 2014.

Risks and Uncertainties

The product candidates developed by the Company require approvals from the U.S. Food and Drug Administration or foreign regulatory agencies prior to commercial sales. There can be no assurance that the Company's current and future product candidates will receive the necessary approvals. If the Company fails to successfully complete clinical development and generate results sufficient to file for regulatory approval or is denied approval or approval is delayed, it may have a material adverse impact on the Company's business and its financial statements.

Concentration of Credit Risk and of Significant Suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and cash equivalents. The Company has all cash and cash equivalents balances at two accredited financial institutions, in amounts that exceed federally insured limits. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Income Taxes

The Company accounts for income taxes under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the estimated future tax consequences attributable to differences between financial statement carrying amounts of existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities are measured using enacted rates in effect for the year in which these temporary differences are expected to be recovered or settled. Valuation allowances are provided if based on the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized. During November 2015, the FASB issued ASU 2015-17, Balance Sheet Classification of Deferred Taxes, which simplifies the presentation of deferred income taxes. The Company early adopted ASU 2015-17 effective December 31, 2015 on a prospective basis. Adoption of this ASU resulted in a reclassification of the current deferred tax liability to a non-current deferred tax liability, in the amount of $0.6 million, which is netted with the long-term deferred tax asset in its consolidated balance sheet as of December 31, 2015.

Fair Value Measurements

Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. Financial assets and liabilities carried at fair value are classified and disclosed in one of the following three categories:

Level 1 — Quoted market prices in active markets for identical assets or liabilities.

Level 2 — Observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities; quoted prices in markets that are not active; or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the assets or liabilities.

Level 3 — Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

The Company's cash equivalents and marketable securities at December 31, 2016 and 2015 were carried at fair value, determined according to the fair value hierarchy; see Footnote 3, Fair Value Measurements.

The carrying amounts reflected in the consolidated balance sheets for accounts payable and accrued expenses approximate their fair values due to their short-term maturities at December 31, 2016 and 2015, respectively.

Deferred Offering Costs

The Company capitalizes certain legal, accounting and other third-party fees that are directly associated with in-process equity financings as other assets until such financings are consummated. After consummation of the IPO in July 2014, $2.3 million of these costs were recorded in stockholders' equity as a reduction of additional paid-in capital generated as a result of the IPO. After consummation of the follow-on public offering of common stock in April 2015, $0.5 million of these costs were recorded in stockholders' equity as a reduction of additional paid-in capital generated as a result of the offering. As of December 31, 2015, the Company had recorded deferred offering costs of $0.2 million, which are shown as a non-current asset, that were for the follow-on public offering that was consummated in January 2016. After consummation of the follow-on public offering of common stock in January 2016, $0.6 million of these costs were recorded in stockholders' equity as a reduction of additional paid-in capital generated as a result of the offering.

Segment Data

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's singular focus is on advancing medicines to treat central nervous system disorders, where there are inadequate or no approved existing therapies. All tangible assets are held within the United States.

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. For the year ended December 31, 2016, the difference between net loss and comprehensive loss was the unrealized loss on marketable securities. For the years ended December 31, 2015 and 2014, there was no difference between net loss and comprehensive loss.

Public Offerings

On July 23, 2014, the Company completed the sale of 5,750,000 shares of its common stock in its IPO (the "IPO"), at a price to the public of $18.00 per share, resulting in net proceeds to the Company of $94.0 million after deducting underwriting discounts and commissions and offering costs paid by the Company. The shares began trading on Nasdaq Global Market on July 18, 2014.

In connection with preparing for the IPO, the Company's board of directors and stockholders approved a 1-for-3.15 reverse stock split of the Company's common stock effective July 2, 2014. All share and per share amounts in the financial statements contained herein and notes thereto have been retroactively adjusted, where necessary, to give effect to this reverse stock split. In connection with the closing of the IPO, all of the Company's outstanding redeemable convertible preferred stock automatically converted into shares of common stock as of July 23, 2014, resulting in the issuance by the Company of an additional 18,007,575 shares of common stock. The significant increase in common stock outstanding in July 2014 will impact the year-over-year comparability of the Company's net loss per share calculations over the next year.

On April 20, 2015, the Company completed the sale of 2,628,571 shares of its common stock at a price to the public of $52.50 per share, resulting in net proceeds to the Company of $129.1 million after deducting underwriting discounts and commissions and offering costs paid by the Company.

On January 12, 2016, the Company completed the sale of 3,157,894 shares of its common stock at a price to the public of $47.50 per share, resulting in net proceeds to the Company of $140.4 million after deducting underwriting discounts and commissions and offering costs paid by the Company.

On September 14, 2016, the Company completed the sale of 5,062,892 shares of its common stock at a price to the public of $39.75 per share, resulting in net proceeds to the Company of $189.2 million after deducting underwriting discounts and commissions and offering costs paid by the Company.

Recently Issued Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board (the "FASB") issued ASU No. 2014-09, *Revenue from Contracts with Customers* (Topic 606), which supersedes all existing revenue recognition requirements, including most industry-specific guidance. The new standard requires a company to recognize revenue when it transfers goods or services to customers in an amount that reflects the consideration that the company expects to receive for those goods or services. The FASB has continued to issue accounting standards updates to clarify and provide implementation guidance related to Revenue from Contracts with Customers, including ASU

2016-08*, Revenue from Contract with Customers: Principal versus Agent Considerations*, ASU 2016-10, *Revenue from Contracts with Customers: Identifying Performance Obligations and Licensing*, and ASU 2016-12, *Revenue from Contracts with Customers: Narrow-Scope Improvements and Practical Expedients.* These amendments address a number of areas, including the entity's identification of its performance obligations in a contract, collectability, non-cash consideration, presentation of sales tax and an entity's evaluation of the nature of its promise to grant a license of intellectual property and whether or not that revenue is recognized over time or at a point in time. These new standards will be effective for the Company beginning January 1, 2018. The Company could early adopt the standard for the year ending December 31, 2017. The Company plans to early adopt the standard as of January 1, 2017, although there is no impact of this new guidance on its consolidated financial statements as it does not currently have any revenue generating arrangements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases*, which will replace the existing guidance in ASC 840, "Leases." The updated standard aims to increase transparency and comparability among organizations by requiring lessees to recognize leased assets and leased liabilities on the consolidated balance sheets and requiring disclosure of key information about leasing arrangements. The standard will be effective on January 1, 2019, with early adoption permitted. The Company is in the process of evaluating the impact that this new guidance will have on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, *Improvements to Employee Share-Based Payment Accounting*, which intends to simplify several aspects of accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, an option to recognize gross stock compensation expense with actual forfeitures recognized as they occur, as well as certain classifications on the statement of cash flows. The standard will be effective on January 1, 2017. The Company is in the process of evaluating the impact that this new guidance will have on its consolidated financial statements.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments,* which introduces a new methodology for accounting for credit losses on financial instruments, including available-for-sale debt securities. The guidance establishes a new "expected loss model" that requires entities to estimate current expected credit losses on financial instruments by using all practical and relevant information. Any expected credit losses are to be reflected as allowances rather than reductions in the amortized cost of available-for-sale debt securities. Early adoption is permitted for annual periods beginning after December 15, 2018, and interim periods therein. The Company is in the process of evaluating the impact that this new guidance will have on its consolidated financial statements.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230): Classification of Certain Cash Receipts and Cash Payments*. The standard reduces the diversity in practice in how certain cash receipts and cash payments are presented and classified in the statement of cash flows. The standard will be effective on January 1, 2018. The Company is in the process of evaluating the impact that this new guidance will have on its consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* that changes the presentation of restricted cash and cash equivalents on the statement of cash flows. Restricted cash and restricted cash equivalents will be included with cash and cash equivalents when reconciling the beginning-of-period and end-of-period total amounts shown on the statement of cash flows. This standard is effective for the Company in the fiscal year beginning January 1, 2018, but early adoption is permissible. The Company is in the process of evaluating the impact that this new guidance will have on its consolidated financial statements. After adopting the standard, the amounts of restricted cash shown on the consolidated balance sheets would be included in cash and cash equivalents in the statement of cash flows.

Other accounting standards that have been issued or proposed by the FASB or other standards-setting bodies that do not require adoption until a future date are not expected to have a material impact on the Company's consolidated financial statements upon adoption.

3. Fair Value Measurements

The Company's cash equivalents are generally classified within Level 1 of the fair value hierarchy. The Company's investments in marketable securities are classified within Level 2 of the fair value hierarchy.

The fair values of the Company's marketable securities are generally based on prices obtained from independent pricing sources. Consistent with the fair value hierarchy described above, securities with validated quotes from pricing services are generally reflected within Level 2, as they are primarily based on observable pricing for similar assets or other market observable inputs. Typical inputs used by these pricing services include, but are not limited to, reported trades, benchmark yields, issuer spreads, bids, offers or estimates of cash flow, prepayment spreads and default rates.

The following tables summarize the Company's money market funds and marketable securities as of December 31, 2016 and 2015:

	December 31, 2016			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Money market funds	$ 168,517	$ 168,517	$ —	$ —
Total cash equivalents	168,517	168,517	—	—
Marketable securities:				
U.S. government securities	100,031	—	100,031	—
U.S. corporate bonds	58,452	—	58,452	—
International corporate bonds	24,190	—	24,190	—
U.S. commercial paper	30,351	—	30,351	—
International commercial paper	15,938	—	15,938	—
Total marketable securities	228,962	—	228,962	—
Total cash equivalents and marketable securities	$ 397,479	$ 168,517	$ 228,962	$ —

	December 31, 2015			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash and cash equivalents:				
Money market funds	$ 186,753	$ 186,753	$ —	$ —
Total cash and cash equivalents	$ 186,753	$ 186,753	$ —	$ —

During the years ended December 31, 2016 and 2015, there were no transfers among the Level 1, Level 2 and Level 3 categories.

Marketable Securities

The following table summarizes the Company's marketable securities as of December 31, 2016:

	December 31, 2016			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
U.S. government securities (due within 1 year)	$ 100,055	$ 2	$ (26)	$ 100,031
U.S. corporate bonds	58,508	—	(56)	58,452
International corporate bonds	24,212	—	(22)	24,190
U.S. commercial paper	30,351	—	—	30,351
International commercial paper	15,938	—	—	15,938
	$ 229,064	$ 2	$ (104)	$ 228,962

The Company held no marketable securities as of December 31, 2015.

As of December 31, 2016, all marketable securities held by the Company had remaining contractual maturities of one year or less.

As of December 31, 2016, the Company held 27 marketable securities which were in a loss position due to fluctuations in interest rates for less than one year.

There have been no impairments of the Company's assets measured and carried at fair value during the years ended December 31, 2016 and 2015.

4. Balance Sheet Components

Property and Equipment, net

Property and equipment, net consists of the following:

	December 31,	
	2016	2015
	(in thousands)	
Computer hardware and software	$ 708	$ 400
Furniture and equipment	695	147
Leasehold improvements	527	-
	1,930	547
Less: Accumulated depreciation	(542)	(261)
Property and equipment, net	$ 1,388	$ 286

Depreciation expense for the years ended December 31, 2016, 2015 and 2014 was $0.3 million, $0.1 million and $0.1 million, respectively.

The useful life for computer hardware and software is 3 years; furniture and equipment is 5 years; and leasehold improvements is the lesser of the useful life of the term of the respective lease.

Accrued Expenses

Accrued expenses consist of the following:

	December 31,	
	2016	2015
	(in thousands)	
Development costs	$ 14,541	$ 6,466
Employee-related expenses	5,948	2,718
Professional services	1,751	935
Other accrued expenses	112	29
	$ 22,352	$ 10,148

5. Commitments and Contingencies

Operating Leases

The Company rents 22,067 square feet of office space in a multi-tenant building under an operating lease that will expire in February 2022. In May 2016, the Company entered into a lease under which, beginning in September 2016, the Company rents 19,805 square feet of additional office space, in a separate multi-tenant building. The lease for the additional space will expire in February 2022.

Rent expense, net of sublease income, for the years ended December 31, 2016, 2015 and 2014, was $2.0 million, $0.4 million, and $0.3 million, respectively.

Future minimum lease payments under non-cancelable operating leases are as follows at December 31, 2016:

Years Ending December 31,	(in thousands)
2017	$ 2,666
2018	2,729
2019	2,771
2020	2,813
2021	2,855
Thereafter	480
	$ 14,314

License Agreements

CyDex License Agreement

In September 2015, the Company and CyDex Pharmaceuticals, Inc. ("CyDex") amended and restated their existing commercial license agreement. Under the terms of the commercial license agreement as amended and restated, CyDex has granted to the Company an exclusive license to CyDex's Captisol drug formulation technology and related intellectual property for the manufacture of pharmaceutical products incorporating the Company's compounds known as SAGE-547 and SAGE-689, and the development and commercialization of the resulting products in the treatment, prevention or diagnosis of any disease or symptom in humans or animals other than (i) the ocular treatment of any disease or condition with a formulation, including a hormone; (ii) topical ocular treatment of inflammatory conditions; (iii) treatment and prophylaxis of fungal infections in humans; and (iv) any ocular treatment for retinal degeneration.

As consideration for the inclusion of SAGE-689 in the license granted by CyDex, the Company paid to CyDex $0.1 million, which was recorded as research and development expense for the three months ended September 30, 2015 in connection with the execution of the amended and restated license agreement.

The Company is obligated to make milestone payments under the amended and restated license agreement with CyDex based on the achievement of clinical development and regulatory milestones in the amount of up to $0.8 million in clinical milestones and up to $3.8 million in regulatory milestones for each of the first two fields with respect to SAGE-547; up to $1.3 million in clinical milestones and up to $8.5 million in regulatory milestones for each of the third and fourth fields with respect to SAGE-547; and up to $0.8 million in clinical milestones and up to $1.8 million in regulatory milestones for one field with respect to SAGE-689.

For the year ended December 31, 2016, additional clinical development milestones were met for the SAGE-547 program under the license agreement with CyDex, and accordingly, the Company recorded research and development expense and made cash payments totaling $0.8 million.

For the year ended December 31, 2015, additional clinical development milestones were met for the SAGE-547 program under the license agreement with CyDex, and accordingly, the Company recorded research and development expense and made cash payments totaling $0.8 million.

Washington University License Agreement

In November 2013, the Company entered into a license agreement with Washington University whereby the Company was granted exclusive, worldwide rights to develop and commercialize a novel set of neuroactive steroids developed by Washington University. In exchange for development and commercialization rights, the Company paid an upfront, non-refundable payment of $50,000 and is required to pay an annual license maintenance fee of $15,000 on each subsequent anniversary date, until the first Phase 2 clinical trial for a licensed product is initiated. The Company is obligated to make milestone payments to Washington University based on achievement of clinical development and regulatory milestones of up to $0.7 million and $0.5 million, respectively. Additionally, the Company fulfilled its obligation to issue to Washington University 47,619 shares of common stock on December 13, 2013. The fair value of these shares of $0.1 million was recorded as research and development expense in 2013.

The Company is obligated to pay royalties to Washington University at rates in the low single digits on net sales of licensed products covered under patent rights and royalties at rates in the low single digits on net sales of licensed products not covered under patent rights. Additionally, the Company has the right to sublicense and is required to make payments at varying percentages of sublicensing revenue received, initially in the mid-teens and descending to the mid-single digits over time.

For the year ended December 31, 2016, the Company did not record any expense or make any milestone payments under the license agreement with Washington University

For the year ended December 31, 2015, a regulatory milestone was met for one of the programs under the license agreement with Washington University, and accordingly, the Company recorded research and development expenses and made a cash payment of $50,000.

University of California License Agreement

In October 2013, the Company entered into a non-exclusive license agreement with The Regents of the University of California whereby the Company was granted a non-exclusive license to certain clinical data and clinical material for use in the development and commercialization of biopharmaceutical products in the licensed field, including status epilepticus and post-partum depression. In May 2014, the license agreement was amended to add the treatment of essential tremor to the licensed field of use, materials and milestone fee provisions of the agreement. The Company paid to The Regents of the University of California clinical development milestones of up to $0.1 million and will be required to pay royalties of less than 1% on net sales for a period of fifteen years following the sale of the first product. The license will terminate on the earlier to occur of (i) 27 years after the effective date or (ii) 15 years after the last-derived product is first commercially sold.

For the years ended December 31, 2014 and 2013, the Company did not record any expense or make any milestone or royalty payments under the license agreement with the University of California.

In June 2015, the Company entered into an exclusive license agreement with The Regents of the University of California whereby the Company was granted an exclusive license to certain patent rights related to the use of allopregnanolone to treat various diseases. In exchange for such license, the Company paid an upfront payment of $50,000 and will make payments of $15,000 for annual maintenance fees until the calendar year following the first sale, if any, of a licensed product. The Company is obligated to make milestone payments following the achievement of specified regulatory and sales milestones of up to $0.7 million and $2.0 million in the aggregate, respectively. Following the first sale, if any, of a licensed product, the Company is obligated to pay royalties at a low single digit percentage of net sales, if any, of licensed products, subject to specified minimum annual royalty amounts. Unless terminated by operation of law or by acts of the parties under the terms of the agreement, the license agreement will terminate when the last-to-expire patents or last-to-be abandoned patent applications expire, whichever is later.

For the year ended December 31, 2015, three clinical development milestones were met, and accordingly, the Company recorded research and development expenses and made cash payments totaling $0.1 million.

For the year ended December 31, 2016, the Company did not record any expense or make any milestone or royalty payments under either license agreement with The Regents of the University of California.

Consulting Agreement

In January 2014, the Company entered into a consulting agreement with a non-employee advisor whereby the Company is obligated to make cash payments of up to $2.0 million and to issue up to 126,984 shares of common stock upon attainment of certain clinical development and regulatory milestones.

In January and March 2014, the first clinical development milestones for each of two programs included in the consulting agreement were met. Accordingly, the Company recorded research and development expense for the year ended December 31, 2014 of $0.2 million, comprised of $50,000 in cash and $0.1 million related to the issuance of 15,872 shares of the Company's common stock.

For the year ended December 31, 2015, the second and third clinical development milestones for one of the programs included in the consulting agreement were met. Accordingly, the Company recorded research and development expense for the year ended December 31, 2015 of $1.7 million, comprised of $0.5 million in cash and $1.2 million related to the issuance of 23,809 shares of the Company's common stock, related to the achievement of these milestones.

For the year ended December 31, 2016, the Company did not record any expense or make any milestone payments under the consulting agreement with the non-employee advisor.

6. Preferred Stock

As of December 31, 2016 and 2015, the Company has authorized 5,000,000 shares of preferred stock. The preferred stock was classified under stockholders' equity (deficit) as of December 31, 2016 and 2015.

The Company had issued Series A, Series B and Series C redeemable convertible preferred stock (collectively, the "Redeemable Preferred Stock"). The Redeemable Preferred Stock was classified outside of stockholders' equity (deficit) as of December 31, 2013 because the shares contained redemption features that are not solely within the control of the Company. In July 2014, all issued and outstanding Redeemable Preferred Stock was converted to common stock, see Note 2.

7. Common Stock

As of December 31, 2016 and 2015, the Company has authorized 120,000,000 shares of common stock with a par value of $0.0001 per share.

Each share of common stock entitles the holder to one vote on all matters submitted to a vote of the Company's stockholders. Common stockholders are entitled to receive dividends, as may be declared by the Board of Directors, if any. As of December 31, 2016 and 2015, no dividends have been declared.

During the year ended December 31, 2016, the Company received 346 shares of the Company's common stock from an employee as proceeds for an exercise of stock options. The total cost of shares held in treasury at December 31, 2016 was $17,000.

8. Stock-Based Compensation

Stock Option Plans

On July 2, 2014, the Company's stockholders approved the 2014 Stock Option and Incentive Plan (the "2014 Stock Option Plan"), which became effective upon the completion of the IPO. The 2014 Stock Option Plan provides for the grant of restricted stock awards, restricted stock units, incentive stock options and non-statutory stock options. The 2014 Stock Option Plan replaced the Company's 2011 Stock Option and Grant Plan (the "2011 Stock Option Plan"). The Company will no longer grant stock options or other awards under the 2011 Stock Option Plan. Any options or awards outstanding under the 2011 Stock Option Plan remained outstanding and effective. As of December 31, 2016, the total number of shares reserved under all equity plans is 4,891,922, and the Company had 660,115 shares available for future issuance under such plans. On December 15, 2016, the Board of Directors of the Company approved the 2016 Inducement Equity Plan, for which no grants were made as of December 31, 2016.

The 2014 Stock Option Plan provides for an annual increase, to be added on the first day of each fiscal year, by up to 4% of the Company's issued and outstanding shares of common stock on the last day of the prior fiscal year. On January 1, 2017, 1,488,886 shares of common stock, representing 4% of the Company's issued and outstanding shares of common stock as of December 31, 2016, were added to the 2014 Stock Option Plan.

Terms of restricted stock awards, restricted stock units, and stock option agreements, including vesting requirements, are determined by the Board of Directors or the Compensation Committee of the Board of Directors, subject to the provisions of the applicable stock option plan. Options and restricted stock awards granted by the Company, that are not performance-based, generally vest based on the continued service of the grantee with the Company during a specified period following grant. These awards, when granted to employees, generally vest ratably over four years, with a 25% cliff vesting at the one year anniversary. All option awards expire in 10 years.

During the years ended December 31, 2016 and 2015, the Company granted 74,039 and 497,100 options, respectively, to employees to purchase shares of common stock that contain performance-based vesting criteria, primarily related to achievement of certain clinical and regulatory development milestones related to product candidates. Recognition of stock-based compensation expense associated with these performance-based stock options commences when the performance condition is considered probable of achievement, using management's best estimates.

During the year ended December 31, 2015, one milestone was achieved. This milestone represents 35% of the performance-based option grants that were made during the year ended December 31, 2015. During the year ended December 31, 2015, the Company recognized stock-based compensation expense related to this milestone of $4.8 million.

During the year ended December 31, 2016, one milestone was achieved. This milestone represents 50% and 30%, of the performance-based option grants that were made during the years ended December 31, 2016 and 2015, respectively. During the year ended December 31, 2016, the Company recognized stock-based compensation expense related to this milestone of $5.0 million.

The achievement of the remaining milestones was deemed to be not probable as of December 31, 2016, and therefore no expense has been recognized related to these awards for the year ended December 31, 2016.

Stock-based compensation expense recognized during the years ended December 31, 2016, 2015 and 2014 was as follows:

	Year Ended December 31,		
	2016	2015	2014
		(in thousands)	
Research and development	$ 11,197	$ 5,924	$ 1,093
General and administrative	11,823	9,316	1,419
	$ 23,020	$ 15,240	$ 2,512

During the years ended December 31, 2016 and 2015, the Company recorded $0.2 million and $0.1 million, respectively, of stock-based compensation expense related to the Employee Stock Purchase Plan.

For stock option awards, the fair value is estimated at the grant date using the Black-Scholes option-pricing model, taking into account the terms and conditions upon which options are granted. The fair value of the options is amortized on a straight-line basis for awards to employees and on a graded basis for awards to non-employees over the requisite service period of the awards. The weighted average grant date fair value per share relating to outstanding stock options granted under the Company's stock option plans during the years ended December 31, 2016, 2015 and 2014 was $24.97, $34.08 and $14.33, respectively.

The fair value of each option granted to employees and nonemployee directors during the years ended December 31, 2016, 2015 and 2014 under the Company's stock option plans has been calculated on the date of grant using the following weighted average assumptions:

	Year Ended December 31,		
	2016	2015	2014
Expected dividend yield	0%	0%	0%
Expected volatility	80.15%	90.54%	98.86%
Risk-free interest rate	1.47%	1.59%	1.95%
Expected life of option	6.05 years	6.03 years	6.38 years

Expected dividend yield: the Company has not paid, and does not anticipate paying, any dividends in the foreseeable future.

Risk-free interest rate: the Company determined the risk-free interest rate by using a weighted average equivalent to the expected term based on the U.S. Treasury yield curve in effect as of the date of grant.

Expected volatility: the Company does not have sufficient history to support a calculation of volatility using only its historical data. Starting in 2016, the Company uses a weighted-average volatility considering the Company's own volatility since the IPO in July 2014 and the volatilities of a peer group of comparable companies for time periods prior to the IPO. Prior to 2016, the Company used volatilities based on an analysis of reported data for a peer group of comparable companies.

Expected term (in years): the expected term represents the period that the Company's stock option grants are expected to be outstanding. The Company has been publicly traded since July 2014, and there is not sufficient historical term data to calculate the expected term of the options. Therefore, the Company elected to utilize the "simplified" method to estimate the expected term of options granted to employees. Under this approach, the weighted average expected life is presumed to be the average of the vesting term and the contractual term of the option.

Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from estimates. The Company estimates forfeitures based on historical termination behavior. For the years ended December 31, 2016, 2015 and 2014, forfeiture rates of 9.58%, 10% and 10%, respectively, were applied.

For options granted to non-employees, the expected life of the option used is 10 years, which is the contractual term of each option. All other assumptions used to calculate the grant date fair value are generally consistent with the assumptions used for options granted to employees.

The table below summarizes activity related to stock options:

	Shares	Weighted Average Exercise Price	Weighted Average Remaining Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding as of December 31, 2015	3,002,809	$ 26.67	8.67	$ 96,479
Granted	1,454,568	35.98		
Exercised	(124,903)	8.09		
Forfeited	(100,667)	44.76		
Outstanding as of December 31, 2016	4,231,807	$ 29.99	8.24	$ 92,843
Vested and expected to vest as of December 31, 2016	3,727,837	$ 29.36	8.21	$ 84,395
Vested and exercisable as of December 31, 2016	1,702,819	$ 24.11	7.59	$ 48,096

As of December 31, 2016, the Company had unrecognized stock-based compensation expense related to its unvested service-based stock option awards of $43.6 million, which is expected to be recognized over the remaining weighted average vesting period of 2.77 years. The total fair value of options vested for the years ended December 31, 2016, 2015 and 2014 was $24.1 million, $9.2 million, and $1.0 million, respectively.

In addition, the Company granted 245,872 stock options that are both outstanding and unvested that will vest upon the achievement of certain performance criteria in the future. Total unrecognized stock-based compensation expense related to those awards was $5.2 million at December 31, 2016.

The intrinsic value of stock options exercised during the years ended December 31, 2016, 2015 and 2014 was $4.6 million, $28.4 million and $2.4 million, respectively.

Restricted Stock Awards

During the years ended December 31, 2013, 2012 and 2011, the Company granted restricted stock awards to certain officers, employees, directors, and consultants of the Company.

The table below summarizes activity relating to restricted stock:

	Shares
Outstanding as of December 31, 2015	42,781
Issued	—
Vested	(42,781)
Forfeited	—
Repurchased	—
Outstanding as of December 31, 2016	—

As of December 31, 2016, all of the restricted stock was vested.

2014 Employee Stock Purchase Plan

On July 2, 2014, the Company's stockholders approved the 2014 Employee Stock Purchase Plan, which had been previously approved by the Board of Directors. A total of 282,000 shares of common stock were initially authorized for issuance under this plan. The 2014 Employee Stock Purchase Plan became effective upon the completion of the IPO. As of December 31, 2016, 14,351 shares have been issued under this plan. At December 31, 2016, accrued expenses includes $67,000 of stock-based compensation expense related to an enrollment period for which the related shares had not been issued as of December 31, 2016.

9. Net Loss Per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows for the years ended December 31, 2016, 2015 and 2014:

	Year Ended December 31,		
	2016	2015	2014
Basic net loss per share attributable to common stockholders:			
Numerator:			
Net loss attributable to common stockholders (in thousands)	$ (158,987)	$ (94,495)	$ (36,105)
Denominator:			
Weighted average common stock outstanding—basic	33,492,795	27,778,288	21,574,347
Dilutive effect of shares of common stock equivalents resulting from common stock options and preferred common stock (as converted)	—	—	—
Weighted average common stock outstanding—diluted	33,492,795	27,778,288	21,574,347
Net loss per share attributable to common stockholders—basic and diluted	$ (4.75)	$ (3.40)	$ (1.67)

The following common stock equivalents outstanding as of December 31, 2016 and 2015 were excluded from the computation of diluted net loss per share for the periods presented because including them would have been anti-dilutive:

	Year Ended December 31,	
	2016	2015
Stock options	3,985,935	2,643,833
Employee stock purchase plan	6,784	3,307
Restricted stock	—	42,781
	3,992,719	2,689,921

10. Income Taxes

There is no provision for income taxes because the Company has historically incurred operating losses and maintains a full valuation allowance against its net deferred tax assets. The reported amount of income tax expense for the years differs from the amount that would result from applying domestic federal statutory tax rates to pretax losses primarily because of changes in valuation allowance.

A reconciliation of U.S. statutory rate to the Company's effective tax rate is as follows:

	Year Ended December 31,		
	2016	2015	2014
Tax at Statutory Rate	34.0%	34.0%	34.0%
State Taxes, net of federal benefit	4.2	4.0	4.5
Permanent Items	(1.0)	(0.9)	(1.0)
Orphan Drug Credit Addback	(2.9)	(4.2)	—
Foreign Rate Differential	(3.1)	(3.1)	—
Federal and State Credits	10.3	13.2	8.5
Change in Valuation Allowance	(41.5)	(43.1)	(46.0)
Other	—	0.1	—
	0.0%	0.0%	0.0%

Significant components of the Company's net deferred tax asset at December 31, 2016 and 2015 are as follows:

	December 31,	
	2016	2015
	(in thousands)	
Net operating losses	$ 84,374	$ 44,172
Capitalized start-up costs	2,155	2,335
Accounting method change	(673)	(1,347)
Tax credit carryforwards	33,477	17,013
Accrued expenses	2,287	1,062
Depreciation and amortization	999	716
Stock options	12,103	5,097
Others	350	21
Total net deferred tax asset before valuation allowance	135,072	69,069
Valuation allowance	(135,072)	(69,069)
Net deferred tax asset	$ -	$ -

As of December 31, 2016, the Company had federal and state net operating loss carryforwards of $235.4 million and $234.3 million, respectively, which begin to expire in 2031. As of December 31, 2016, the Company had federal and state research and development tax credits carryforwards of $4.1 million and $1.6 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2016, the Company had federal orphan drug tax credit carry forwards of $29.8 million, which begin to expire in 2034. At December 31, 2016, the Company has excess equity based compensation tax deductions related to net operating losses for federal and state purposes of $20.4 million and $20.4 million respectively. The Company has excess equity based compensation related to credits for federal and state purposes of $1.3 million and $0.2 million, respectively. These excess tax benefits have not been included in the net deferred tax assets before valuation allowance since these benefits would be credited directly to additional paid in capital if subsequently recognized through a reduction in taxes payable.

The deferred tax assets above exclude $8.0 million of net operating losses and $1.5 million of federal and state research and development credits related to tax deductions from the exercise of stock options subsequent to the adoption of the 2006 accounting standard on stock-based compensation. This amount represents an excess tax benefit and has not been included in the gross deferred tax assets. The Company will adopt ASU 2016-09, Improvements to Employee Share-Based Payment Accounting, for the quarter ended March 31, 2017. As a result of adoption, the deferred tax assets associated with net operating losses will increase by $8.0 million and the deferred tax assets associated with federal and state research credits will increase by $1.5 million. These amounts will be offset by a corresponding increase in the valuation allowance. The adoption of ASU 2016-09 will have no impact to the Company's income statement, balance sheet, or retained earnings.

As of December 31, 2016, net deferred tax assets increased approximately $66.0 million primarily due to the operating loss and tax credits incurred during the year. This increase in net deferred tax assets was offset by a corresponding increase in the valuation allowance.

Management of the Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets, which are comprised principally of net operating loss carryforwards and tax credit carryforwards. Under the applicable accounting standards, management has considered the Company's history of losses and concluded that it is more likely than not that the Company will not recognize the benefits of federal and state deferred tax assets. Accordingly, a full valuation allowance of $135.1 million and $69.1 million has been established at December 31, 2016 and 2015, respectively.

Pursuant to Section 382 of the Internal Revenue Code, certain substantial changes in the Company's ownership may result in a limitation on the amount of net operating loss carryforwards and tax carryforwards that may be used in future years. Utilization of the net operating loss ("NOL") and tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986 due to ownership change limitations that have occurred previously or that could occur in the future. These ownership changes may limit the amount of NOL and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. The Company has not completed a study to assess whether an ownership change has occurred, or whether there have been multiple ownership changes since its formation, due to significant complexity and related costs associated with such a study. There could also be additional ownership changes in the future which may result in additional limitations on the utilization of NOL carryforwards and credits. Further, until a study is completed and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company applies the authoritative guidance on accounting for and disclosure of uncertainty in tax positions, which requires the Company to determine whether a tax position of the Company is more likely than not to be sustained upon examination, including resolution of any related appeals of litigation processes, based on the technical merits of the position. For tax positions meeting the more likely than not threshold, the tax amount recognized in the financial statements is reduced by the largest benefit that has a greater than fifty percent likelihood of being realized upon the ultimate settlement with the relevant taxing authority.

The following is a rollforward of the Company's unrecognized tax benefits:

	Year Ended December 31,		
	2016	2015	2014
		(in thousands)	
Unrecognized tax benefits—as of the beginning of the year	$ —	$ —	$ 2,880
Gross increases—current period tax positions	—	—	—
Gross decreases—tax positions of prior periods	—	—	(2,880)
Unrecognized tax benefits—as of the end of the year	$ —	$ —	$ —

During 2014, the Company filed an application for change in accounting method with the IRS to capitalize start-up costs that were historically deducted and included as part of the NOL carryforward through December 31, 2013. As a result, the Company's unrecognized tax benefits, which historically related to start-up costs, are zero at December 31, 2016. The Company has not, as of yet, conducted a study of its R&D credit carryforwards. This study may result in an adjustment to the Company's R&D credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position under Topic 740. A full valuation allowance has been provided against the Company's R&D credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the consolidated balance sheets or statements of operations if an adjustment were required.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense when in a taxable income position. As of December 31, 2016 and 2015, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statement of operations.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations, and the Company's tax returns are open under statute from 2013 to the present. The tax attributes prior to 2013 may still be adjusted upon examination. The Company's policy is to record interest and penalties related to income taxes as part of the tax provision.

During November 2015, the FASB issued ASU 2015-17, Balance Sheet Classification of Deferred Taxes, which simplifies the presentation of deferred income taxes. This ASU requires that deferred tax assets and liabilities be classified as non-current in a statement of financial position. The standard is effective for public companies for fiscal years beginning after December 31, 2016, including interim periods within that reporting period. Early adoption is permitted for any interim and annual financial statements that have not yet been issued. The Company early adopted ASU 2015-17 effective December 31, 2015 on a prospective basis. Adoption of this ASU resulted in a reclassification of the current deferred tax liability to a non-current deferred tax liability, in the amount of $0.6 million, which is netted with the long-term deferred tax asset in its consolidated balance sheet as of December 31, 2015. No prior periods were retrospectively adjusted.

11. Employee Benefit Plan

The Company maintains a 401(k) profit sharing plan (the "Plan") for its employees. Each participant in the Plan may elect to contribute a portion of his or her annual compensation to the Plan subject to annual limits established by the Internal Revenue Service. Effective November 1, 2014, the Company instituted an employer match of 50% of eligible contributions up to 6% of employee contributions. For the years ended December 31, 2016 and 2015, the Company contributed $0.4 million and $0.2 million, respectively.

12. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2016 and 2015. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	2016				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share amounts)				
Total operating expenses	$ 30,714	$ 35,006	$ 38,064	$ 56,379	$ 160,163
Loss from operations	(30,714)	(35,006)	(38,064)	(56,379)	(160,163)
Net loss	(30,543)	(34,747)	(37,796)	$ (55,901)	(158,987)
Net loss per share attributable to common stockholders—basic and diluted	$ (0.97)	$ (1.08)	$ (1.15)	$ (1.50)	$ (4.75)

	2015				
	First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share amounts)				
Total operating expenses	$ 16,897	$ 25,059	$ 24,082	$ 28,612	$ 94,650
Loss from operations	(16,897)	(25,059)	(24,082)	(28,612)	(94,650)
Net loss	(16,871)	(25,027)	(24,035)	(28,562)	(94,495)
Net loss per share attributable to common stockholders—basic and diluted	$ (0.66)	$ (0.90)	$ (0.84)	$ (0.99)	$ (3.40)

Exhibit List

Exhibit No.	Description
3.1	Fifth Amended and Restated Certificate of Incorporation of the Registrant, as currently in effect (incorporated by reference to Exhibit 3.2 of the Registrant's Current Report on Form 8-K (File No. 000-36544) filed on July 25, 2014)
3.2	By-laws of the Registrant and the amendments thereto, as currently in effect (incorporated by reference to Exhibit 3.4 of the Registrant's Current Report on Form 8-K (File No. 000-36544) filed on July 25, 2014)
4.1	Specimen Common Stock Certificate (incorporated by reference to Exhibit 4.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
4.2	Second Amended and Restated Investors' Rights Agreement by and among the Registrant and certain of its stockholders dated March 11, 2014 (incorporated by reference to Exhibit 4.2 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.1+	2014 Stock Option and Incentive Plan and forms of award agreements thereunder (incorporated by reference to Exhibit 10.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.2*	Exclusive License Agreement by and between the Registrant and Washington University, dated November 11, 2013 (incorporated by reference to Exhibit 10.3 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.3*	Amended and Restated Commercial License by and between the Registrant and CyDex Pharmaceuticals, Inc., dated September 25, 2015 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 6, 2015.
10.4*	Non-Exclusive License Agreement by and between the Registrant and the Regents of University of California, dated October 23, 2013, as amended May 14, 2014 (incorporated by reference to Exhibit 10.5 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.5	Lease Agreement, by and between the Registrant and ARE-MA Region No. 38, LLC, dated December 11, 2011, as amended by First Amendment to Lease, by and between ARE-MA Region No. 38, LLC, dated October 26, 2012, and Second Amendment to Lease, by and between ARE-MA Region No. 38, LLC, dated May 9, 2013 (incorporated by reference to Exhibit 10.6 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.6+	Offer letter by and between the Registrant and Jeffrey M. Jonas, dated July 18, 2013 (incorporated by reference to Exhibit 10.7 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.7+	Offer letter by and between the Registrant and Albert J. Robichaud, dated September 25, 2011 (incorporated by reference to Exhibit 10.8 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.8+	Offer letter by and between the Registrant and Stephen J. Kanes, dated May 21, 2013 (incorporated by reference to Exhibit 10.9 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.9+	Offer letter by and between the Registrant and Kimi Iguchi, dated February 7, 2013 (incorporated by reference to Exhibit 10.10 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.10+	Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Jeffrey M. Jonas, dated August 19, 2013 (incorporated by reference to Exhibit 10.11 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.11+	Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Albert J. Robichaud, dated November 7, 2011 (incorporated by reference to Exhibit 10.12 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.12+	Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Stephen J. Kanes, dated July 17, 2013 (incorporated by reference to Exhibit 10.13 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.13+	Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Kimi Iguchi, dated March 8, 2013 (incorporated by reference to Exhibit 10.14 of the Registrant's Registration Statement on Form S-1

Exhibit No.	Description
	(File No. 333-196849) filed on July 8, 2014)
10.14	Form of Indemnification Agreement to be entered into between the Registrant and its directors (incorporated by reference to Exhibit 10.16 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.15	Form of Indemnification Agreement to be entered into between the Registrant and its officers (incorporated by reference to Exhibit 10.17 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.16*	Supply Agreement by and between the Registrant and CyDex Pharmaceuticals, Inc., dated December 13, 2012, as amended August 21, 2013 and April 30, 2014 (incorporated by reference to Exhibit 10.18 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.17+	2014 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.19 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.18+	Offer Letter by and between the Registrant and Thomas D. Anderson, dated April 15, 2014 (incorporated by reference to Exhibit 10.20 of the Registrant's Registration Statement on Form S-1 (File No. 333-196849) filed on July 8, 2014)
10.19+	Severance and Change In Control Agreement between the Registrant and Jeffrey M. Jonas, dated September 25, 2014 (incorporated by reference to Exhibit 10.20 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on March 6, 2015)
10.20+	Severance and Change In Control Agreement between the Registrant and Kimi Iguchi, dated September 30, 2014 (incorporated by reference to Exhibit 10.21 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on March 6, 2015)
10.21+	Severance and Change In Control Agreement between the Registrant and Stephen J. Kanes, dated September 30, 2014 (incorporated by reference to Exhibit 10.22 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on March 6, 2015)
10.22+	Severance and Change In Control Agreement between the Registrant and Albert J. Robichaud, dated September 25, 2014 (incorporated by reference to Exhibit 10.23 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on March 6, 2015)
10.23+	Severance and Change In Control Agreement between the Registrant and Thomas D. Anderson, dated September 26, 2014 (incorporated by reference to Exhibit 10.24 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on March 6, 2015)
10.24*	Exclusive License Agreement by and between the Registrant and the Regents of the University of California, dated June 6, 2015 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q/A (File No. 001-36544) filed on October 31, 2015)
10.25	Third Amendment to Lease, by and between Registrant and ARE-MA Region No. 38, LLC, dated as of September 9, 2015 (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 6, 2015)
10.26	Fourth Amendment to Lease, by and between the Registrant and ARE-MA Region No. 38, LLC, dated as of October 27, 2015 (incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 6, 2015)
10.27	Amendment No. 3 to Supply Agreement, by and between the Registrant and CyDex Pharmaceuticals, Inc., dated September 25, 2015 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 6, 2015)
10.28	Fifth Amendment to Lease, by and between the Registrant and ARE-MA Region No. 38, LLC, dated as of December 9, 2015 (incorporated by reference to Exhibit 10.29 of the Registrant's Annual Report on Form 10-K (File No. 001-36544) filed on February 29, 2016)
10.29	Lease Agreement, by and between the Registrant and Jamestown Premier 245 First, LLC, dated May 24, 2016 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 9, 2016)

Exhibit No.	Description
10.30+	2016 Annual Bonus Incentive Plan (incorporated by reference to Exhibit 10.1 of the Registrant's Current Report on Form 8-K (File No. 001-36544) filed on May 3, 2016)
10.31+	2016 Inducement Equity Plan (incorporated by reference to Exhibit 99.2 of the Registrant's Form S-8 (File No. 333-216202) filed on February 23, 2017)
10.32+	Amended and Restated Non-employee Director Compensation Plan
21.1	Subsidiaries of the Registrant
23.1	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm
31.1	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1**	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Labels Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Link Document

(+) Management contract or compensatory plan or arrangement.

(*) Confidential treatment has been granted by the Securities and Exchange Commission as to certain portions.

(**) The certifications furnished in Exhibit 32.1 hereto are deemed to accompany this Annual Report on Form 10-K and will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended. Such certifications will not be deemed to be incorporated by reference into any filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

Sage Therapeutics is a clinical-stage biopharmaceutical company committed to developing novel medicines to transform the lives of patients with life-altering central nervous system (CNS) disorders.

EXECUTIVE LEADERSHIP

JEFF JONAS, M.D.
Chief Executive Officer

MICHAEL CLOONAN
Chief Business Officer

JIM DOHERTY, Ph.D.
Chief Research Officer

STEVE KANES, M.D., Ph.D.
Chief Medical Officer

KIMI IGUCHI
Chief Financial Officer

AL ROBICHAUD, Ph.D.
Chief Scientific Officer

ANNE MARIE COOK, J.D.
SVP, General Counsel

ERIN LANCIANI
SVP, People and Organizational Strategy

AMY SCHACTERLE, Ph.D.
SVP, Regulatory Affairs and Quality Assurance

HEINRICH SCHLIEKER, Ph.D.
SVP, Technical Operations

BOARD OF DIRECTORS

KEVIN STARR
JEFF JONAS, M.D.
STEVEN PAUL, M.D.
HOWARD H. PIEN
JAMES M. FRATES
MICHAEL C. COLA
GENO GERMANO

SAGE THERAPEUTICS

ANNUAL MEETING

THE ANNUAL MEETING OF STOCKHOLDERS will be held at 9:00 a.m. EDT on June 7, 2017 at
Sage Therapeutics
215 First Street
Cambridge, MA 02142

INDEPENDENT AUDITORS

PRICEWATERHOUSECOOPERS LLC
125 High Street
Boston, MA 02110
(617) 530–5000

INVESTOR INQUIRIES

Email: ir@sagerx.com
Phone: (617) 299–8377

STOCK LISTING

NASDAQ: SAGE

TRANSFER AGENT

The transfer agent is responsible, among other things, for handling stockholder questions regarding lost stock certificates, address changes, including duplicate mailings, and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address:

COMPUTERSHARE TRUST COMPANY
250 Royall Street
Canton, MA 02021
http://www.computershare.com/us/contact/

SEC FORM 10-K

A copy of Sage's annual report on Form 10-K filed with the Securities and Exchange Commission is available free of charge from the company's Investor Relations Department by calling (617) 299-8377, emailing ir@sagerx.com or sending a written request to Sage's Investor Relations Department at:

INVESTOR RELATIONS
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