Sage Therapeutics, Inc.
Form 10-K
February 19, 2019

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, 2018

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	(I.R.S. Employer
Incorporation or Organization)	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 every Interactive Data File required to be submitted 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 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, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	Accelerated filer
Non-accelerated filer	Smaller reporting company
Emerging Growth Company	

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

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, 2018 was approximately $7,110,731,043, 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 12, 2019, there were 47,092,657 shares of common stock, $0.0001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Part III of this Annual Report on Form 10-K incorporates by reference certain information from the registrant's definitive Proxy Statement for its 2019 annual meeting of shareholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2018. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

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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”, “beli “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, and the goals and vision for our business;
- our expectations as to the sufficiency of the data generated from the clinical trials and non-clinical studies of our proprietary intravenous, or IV, formulation of brexanolone, known as ZULRESSO™ (brexanolone) injection, to support approval by the U.S. Food and Drug Administration, or the FDA, of our new drug application, or NDA, for ZULRESSO in the treatment of postpartum depression, or PPD, and the potential timing of such a decision;
- our expectations as to the FDA following the joint recommendation of the Psychopharmacologic Drugs Advisory Committee, or PDAC, and Drug Safety and Risk Management, or DSaRM, Advisory Committee supporting the benefit/risk profile of ZULRESSO in the treatment of PPD when administered in healthcare settings certified under a Risk Evaluation and Mitigation Strategies, or REMS, program;
- our expectations as to the timing of a potential launch of ZULRESSO in the U.S. as a treatment for PPD, if our NDA is approved by the FDA; our views as to our readiness for such a launch; our plans with respect to the size, readiness and focus of our field force; our plans with respect to possible pricing of ZULRESSO; and our expectations with respect to the availability of healthcare facilities qualified and willing to be certified under the REMS as sites of care for administration of ZULRESSO, and the potential for expanding sites of care in the future;
- our views as to the anticipated rate and degree of market acceptance, prescription and use of ZULRESSO, if approved, including the impact of: limitations on sites of care for administration of ZULRESSO to REMS certified healthcare facilities; the risk/benefit profile of ZULRESSO; implementation of the REMS program; pricing; and the potential scope, level and availability of reimbursement;
- our plans to further clarify and evaluate the potential development and regulatory pathway for our proprietary formulation of brexanolone in the European Union, or EU, including our planned activities, and our plans and expectations with respect to the potential development of our other product candidates for markets outside the United States;
- our expectations as to the sufficiency of our planned development program for SAGE-217 in major depressive disorder and PPD, if successful, to support filing of an NDA with the FDA; our statements regarding the potential for approval in such indications in the U.S.; and our view of the potential product profile and market for SAGE-217 and our other product candidates, if successfully developed and approved;
- our ability, within the expected time-frames, to initiate clinical trials and non-clinical studies of existing or future product candidates, including pivotal clinical trials, and to successfully complete and announce the results of ongoing and future clinical trials;
- our estimates regarding expenses, use of cash, potential future revenues, timing of future cash needs, and capital requirements;
- our expectations as to the potential to achieve future revenues, and the potential timing of such revenues;
- our expectations with respect to the availability of supplies of ZULRESSO, SAGE-217 and our other product candidates, and the expected performance of our third-party manufacturers;

- 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 with diseases or disorders of interest to us; the size of the potential markets for our product candidates; the potential for our product candidates in those markets, if approved; and our ability to serve those markets;
- 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 to fund future operations;
- the potential for success of competing products that are or become available for the indications that we are pursuing or may pursue in the future;
- the potential risk of loss of key scientific or management personnel; and
- other risks and uncertainties, including those listed under Part I, 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 business and 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 I, 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.

We may from time to time provide 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. a 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 is ZULRESSO™ (brexanolone) injection, a proprietary intravenous, or IV, formulation of brexanolone for which we have filed a new drug application, or NDA, with the United States Food and Drug Administration, or the FDA, seeking approval to market and sell the product in the treatment of postpartum depression, or PPD. Brexanolone is chemically identical to allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors. PPD is a common biological complication of childbirth, and is characterized by significant depressive symptoms that typically commence during the third trimester of pregnancy or in the months following childbirth. Our NDA for ZULRESSO is currently under FDA review. On November 2, 2018, the Psychopharmacologic Drugs Advisory Committee, or PDAC, and Drug Safety and Risk Management, or DSaRM, Advisory Committee of the FDA jointly voted, by a vote of 17 to 1, that our data support a positive benefit/risk profile for ZULRESSO in the treatment of PPD when administered by qualified staff in a healthcare facility certified under a Risk Evaluation and Mitigation Strategies, or REMS, program. In November 2018, the FDA extended the previously disclosed December 19, 2018 Prescription Drug User Fee Act, or PDUFA, target date for a decision on the NDA for ZULRESSO by a period of three months to March 19, 2019. The launch of ZULRESSO in the U.S., if approved, will follow anticipated scheduling of brexanolone as a controlled substance by the Drug Enforcement Administration, or DEA, which we expect to be completed 90 days after FDA approval. We anticipate that ZULRESSO, if approved, will launch in the U.S. in June 2019.

Our next most advanced product candidate is SAGE-217, an oral compound that is currently in Phase 3 clinical development for PPD and major depressive disorder, or MDD. SAGE-217 is a novel neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. The FDA has granted Breakthrough Therapy designation and Fast Track designation to SAGE-217 in the treatment of MDD. We have completed two positive placebo-controlled pivotal clinical trials with SAGE-217, one in MDD completed in 2017 and one in PPD for which top-line results were reported in January 2019. Our development plan for SAGE-217 is subject to ongoing discussions with the FDA. The ongoing Phase 3 clinical trials for SAGE-217 in MDD are: a placebo-controlled Phase 3 clinical trial in patients with MDD, known as the Mountain Study, in which we are studying two weeks of treatment with SAGE-217 followed by four weeks of follow-up, and an ongoing open-label retreatment study, known as the Shoreline Study, evaluating initial treatment with SAGE-217, treatment-free intervals, and as needed retreatment, in patients with MDD in which patients will be followed for up to a year after treatment. Dosing in the Mountain Study commenced in December 2018, and we expect to report top-line results from this study in the fourth quarter of 2019 or the first quarter of 2020. We plan to add an open-label extension trial to the Mountain Study under a separate protocol to continue to follow patients from the Mountain

Study after completion for up to six months. As part of our Phase 3 clinical development program for SAGE-217 in depression, we also plan to initiate a placebo-controlled trial to evaluate fixed interval SAGE-217 monotherapy (treatment without traditional antidepressants) for up to a year, which we believe will help us meet the expected requirements for a potential NDA filing and inclusion of maintenance dosing as part of the label, if our development efforts are successful. In addition, we are conducting a placebo-controlled polysomnography Phase 3 clinical trial of SAGE-217 in patients with MDD who have co-morbid

insomnia, known as the Rainforest Study. We expect to report top-line results from the Rainforest Study and the Shoreline Study in 2020.

We are also exploring SAGE-217 in other indications, including bipolar depression and sleep disorders. We expect to report topline results from a small open-label Phase 2 clinical trial of SAGE-217 in bipolar depression in the first half of 2019.

In addition to SAGE-217, we have a portfolio of other novel compounds that target $GABA_A$ receptors. SAGE-324 is a novel $GABA_A$ receptor positive allosteric modulator with preclinical pharmacokinetic and pharmacodynamic properties that suggest suitability for chronic oral dosing. We are considering developing SAGE-324 for a number of neurological conditions, including essential tremor and certain epileptiform disorders. Results from a recently completed Phase 1 single ascending dose clinical trial of SAGE-324 demonstrated that the profile of SAGE-324 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. SAGE-324 demonstrated clear target engagement in the brain using pharmaco-EEG (b-band power) as a functional biomarker. SAGE-324 was generally well-tolerated with no serious adverse events and with a safety profile consistent with $GABA_A$ positive allosteric modulation. A Phase 1 multiple ascending dose clinical trial of SAGE-324 is ongoing. We also recently initiated a Phase 1 clinical trial to determine the safety, tolerability and pharmacokinetics of SAGE-324 in a small number of patients with essential tremor. We expect to report top-line results from the Phase 1 multiple ascending dose clinical trial and the Phase 1 essential tremor clinical trial of SAGE-324 in the second half of 2019. Our portfolio also includes SAGE-689, a novel $GABA_A$ receptor positive allosteric modulator, with which we have conducted non-clinical studies to date, and other compounds 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 exploration for potential development of SAGE-718 will be indications involving NMDA receptor hypofunction. Indications involving NMDA receptor hypofunction include certain types, aspects or subpopulations of a number of diseases such as depression, Huntington's disease, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, and neuropathic pain. We completed a Phase 1 single ascending dose trial of SAGE-718 in 2017 and a Phase 1 multiple ascending dose trial in 2018. Results from these Phase 1 clinical trials of SAGE-718 demonstrated that the profile of SAGE-718 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. SAGE-718 was generally well-tolerated with no serious adverse events reported. We are continuing our SAGE-718 Phase 1 clinical program with target engagement biomarker studies in healthy volunteers, focused on electrophysiology and imaging, which are ongoing and for which we expect to report results in the first half of 2019. We also recently initiated a Phase 1 clinical trial to determine the safety, tolerability and pharmacokinetics of SAGE-718 in a small number of patients with early manifest Huntington's disease. We expect to report top-line results from this trial in the second half of 2019.

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, and movement, among others. We believe that we may 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 that have failed in development.

Our Strategy

Our goal is to be the leading biopharmaceutical company focused on development and commercialization of novel proprietary therapies for the treatment of life-altering CNS disorders. Our current focus is on building on our multi-franchise opportunities in depression, neuropsychiatry, and neurology. Key elements of our strategy are to:

- Obtain regulatory approval of ZULRESSO (brexanolone) injection, our proprietary IV formulation of brexanolone in the treatment of PPD in the U.S.;
- Commercialize ZULRESSO in the U.S., if and when approved;
- Advance Phase 3 clinical development of SAGE-217 in MDD; continue to explore SAGE-217 at earlier stages in other indications; and file for regulatory approval of SAGE-217 in the U.S., if our development efforts are successful;
- Support our collaboration with Shionogi & Co., Ltd., or Shionogi, for SAGE-217 in Japan, Taiwan and South Korea, and continue to evaluate opportunities for our product candidates in other global markets;
- Advance SAGE-324 through completion of ongoing Phase 1 clinical trials, with potential future development in essential tremor, certain epileptiform disorders and other neurological conditions;
- Advance SAGE-718 through completion of ongoing Phase 1 clinical trials, with potential future development in indications involving NMDA receptor hypofunction;
- Evaluate the market potential and regulatory pathways for our product candidates in the European Union, or EU, and other countries outside the U.S., and move forward where and when it may make business and strategic sense for us to proceed;
- Advance one or more of our early clinical-stage product candidates into Phase 2 clinical development; and advance one or more of our non-clinical stage compounds into Phase 1 clinical development;
- Bring to market any of our other CNS product candidates that are successfully developed and approved;
- Continue our research and development efforts to evaluate the potential for our existing product candidates in the treatment of additional CNS indications, and the identification of new drug candidates and new areas of interest;
- Enhance the probability of our success by developing unique assets with differentiated features, and focus our internal development activities on indications where we can make well-informed, rapid go/no-go decisions; and
- Utilize the strengths of our proprietary chemistry platform and scientific know-how to expand our portfolio of new chemical entities to lessen our long-term reliance on the success of any one program and to facilitate long-term growth.

Understanding the Foundations of Our Approach

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 to regulate 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.

We are focused on developing drugs based on selective allosteric modulation of neurotransmitter receptors in the CNS. Allosteric modulators are a class of small molecules that interact at a site different from the site where neurotransmitters bind, and allow the potential for fine-tuning of neuronal signals. 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, 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. Our current focus is on 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 in part via activation of $GABA_A$ receptors. $GABA_A$ receptors play a key role in regulating neuron excitability. The NMDA-type receptors of the glutamate receptor system are a major excitatory receptor system in the CNS. NMDA receptors serve a critical role in CNS-related activities. Dysfunction in these systems is implicated in a broad range of CNS disorders.

Our proprietary chemistry platform is centered, as a starting point, on our 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 5,000 compounds. We believe our proprietary chemistry platform allows us to:

- 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 or previous therapies that have failed in development.

We target CNS indications where patient populations are easily identified, clinical endpoints are well-defined, and development pathways are feasible.

Our Product Pipeline

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

ZULRESSO (Brexanolone) Injection

Overview

Our lead product candidate, ZULRESSO (brexanolone) injection, is a proprietary IV formulation of brexanolone that we have developed for the treatment of PPD. Brexanolone is chemically identical to allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors. The FDA is currently reviewing our NDA for this product candidate. On November 2, 2018, the PDAC and DSaRM Advisory Committee of the FDA jointly voted, by a vote of 17 to 1, that our data support a positive benefit/risk profile for ZULRESSO in the treatment of PPD when administered by qualified staff in a healthcare facility certified under a REMS program. The joint recommendations of the PDAC and the DSaRM Advisory Committee are not binding on the FDA. In November 2018, the FDA extended the previously disclosed PDUFA target date for a decision on the NDA for ZULRESSO by a period of three months to March 19, 2019. The launch of ZULRESSO in the U.S., if approved, will follow anticipated scheduling of brexanolone as a controlled substance by the DEA, which we expect to be completed 90 days after FDA approval. We anticipate that ZULRESSO, if approved, will launch in the U.S. in June 2019. We currently have sales, marketing, and market access teams in place in anticipation of a potential launch as well as a patient support team located in Raleigh, North Carolina. If approved, administration of ZULRESSO will be limited to healthcare facilities that have been certified under a REMS program under the supervision of qualified staff to mitigate the potential for harm associated with the risk of excessive sedation and loss of consciousness during the ZULRESSO infusion. As part of the proposed REMS, patients who are prescribed ZULRESSO will be required to enroll in a patient registry to allow us to compile additional information to further our understanding of the risk of excessive sedation and loss of consciousness during administration and management of the risk. Given the mode of administration, the nature of the REMS and the limitation on the administration of ZULRESSO to a healthcare facility setting certified under the REMS, we expect that use of ZULRESSO, if approved for marketing and sale in the U.S., will, at least initially, be focused primarily on women with more severe symptoms of PPD. We estimate that greater than 400,000 women in the U.S. experience PPD symptoms each year of whom approximately 50% are formally diagnosed. We estimate that about 20 to 30% of women diagnosed with PPD experience severe symptoms.

We have received PRIority MEdicines, or PRIME, designation from the European Medicines Agency, or EMA, in the EU for our proprietary formulation of brexanolone as a potential treatment for PPD. In October 2018, we received scientific advice from the EMA regarding the potential regulatory pathway for a marketing authorization application, or MAA, filing in the EU. We anticipate having additional discussions with the EMA to help further clarify and evaluate what additional data and information would be needed, and what other requirements would need to be met, for a potential MAA filing.

Postpartum Depression

PPD is a common biological complication of childbirth, and is characterized by significant depressive symptoms that typically commence during the third trimester of pregnancy or within the months following childbirth. PPD symptoms may 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 baby; and feelings of worthlessness, shame or guilt. In the U.S., estimates of new mothers identified with PPD each year vary state-to-state from 8 to 20 percent, with an overall average of 11.5 percent. Based on these data, we estimate that 400,000 or more women in the U.S. each year may experience PPD, and approximately 50% are formally diagnosed. We estimate that 20 to 30% of women diagnosed with PPD will experience severe symptoms. PPD can lead to devastating consequences for a woman and for her family. Suicide is the leading cause of maternal death following childbirth.

There are no pharmacological therapies specifically approved for PPD. Current standard of care for PPD is comprised of psychotherapy and, in women with moderate or severe PPD, the cautious use of pharmacological therapies such as selective serotonin reuptake inhibitors, or SSRIs, and serotonin and norepinephrine reuptake inhibitors, or SNRIs.

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 after giving birth. Levels of allopregnanolone have been found to be lower in women with PPD than in healthy women. It may be that women with PPD are particularly sensitive to the rapid decline in allopregnanolone after birth, 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 Brexanolone in PPD

In November 2017, we announced positive top-line results from our Hummingbird Phase 3 clinical program studying our proprietary IV formulation of brexanolone in PPD. The Hummingbird Phase 3 program was comprised of two multicenter, randomized, double-blind, parallel-group, placebo-controlled Phase 3 trials designed to evaluate the safety and effectiveness of brexanolone in women with PPD. One study (202B) evaluated women with severe PPD and the other study (202C) evaluated women with moderate PPD, in each case as defined by the study criteria. Entry criteria for participants included symptoms of PPD that began no earlier than the third trimester and no later than the first four weeks following delivery in women who were no more than six months post-partum at the time of screening. In November 2017, we announced that both trials, at all doses, achieved the primary endpoint, a statistically significant mean reduction from baseline in the 17-item Hamilton Rating Scale for Depression, or HAMD-17, total score at 60 hours in the brexanolone group compared to the placebo group (Study 202B: p=0.0252 for 90 μg/kg/h dose and p=0.0013 for 60 μg/kg/h dose; Study 202C: p=0.0160 for 90 μg/kg/h dose).

In Study 202B, 122 women with severe PPD, as measured by a HAMD-17 total score of 26 or above, prior to randomization were dosed in one of three treatment groups: brexanolone 90 μg/kg/hour, brexanolone 60 μg/kg/hour, or placebo, on a 1:1:1 basis. Brexanolone 90 μg/kg/hour treatment was associated with a statistically significant mean reduction in HAMD-17 total score of 17.7 points from baseline at 60 hours compared with a 14.0 point mean reduction in HAMD-17 total score associated with placebo (p=0.0252). Brexanolone 60 μg/kg/hour treatment was associated with a statistically significant mean reduction in HAMD-17 total score of 19.9 points from baseline at 60 hours compared with a 14.0 point mean reduction in HAMD-17 total score associated with placebo (p=0.0013).

Reduction in HAMD-17 total score in the brexanolone group versus placebo were first observed at 48 hours, with statistical significance only in the 60 µg group, and the effect at 60 hours was maintained at the 30-day follow-up period with statistical significance for both brexanolone dose groups. Improvement in the Clinical Global Impression – Improvement, or CGI-I, scale at 60 hours was consistent with the primary endpoint (p=0.0095 for 90 µg/kg/h dose and p=0.0131 for 60 µg/kg/h dose).

In Study 202C, 104 patients with moderate PPD, as measured by a HAMD-17 total score of 20 to 25, were dosed in one of two treatment groups (brexanolone 90 μg/kg/hour or placebo) on a 1:1 basis. Brexanolone treatment was associated with a statistically significant mean reduction in HAMD-17 total score of 14.2 points from baseline at 60 hours (p=0.016) compared with a 12.0 point mean reduction in HAMD-17 total score associated with placebo. Statistical significance was first observed at 48 hours and remained through Day 7, but was not observed at Day 30. However, the effect observed at 60 hours was maintained through the 30-day follow-up period. Improvement in the CGI-I scale at 60 hours was consistent with the primary endpoint (p=0.0005).

Brexanolone IV was generally well tolerated in both trials with similar rates of adverse events across all treatment groups. The most common adverse reactions in the trials were sedation/somnolence, dizziness, dry mouth, flushing and loss of consciousness. Adverse events leading to discontinuation occurred in 2% of patients and were sedation-related or related to infusion site pain. In the Hummingbird program, in patients treated with brexanolone, approximately 4% of patients experienced loss of consciousness and less that 1% experienced an altered state of consciousness during the infusion. All of these patients recovered with dose interruption, and no further intervention was necessary.

The Phase 3 Hummingbird program was an extension of a Phase 2 clinical trial of brexanolone in 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 HAMD-17 score of 26 or above prior to treatment. The trial achieved the primary endpoint of a significant reduction in the HAMD-17 in the brexanolone group 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 brexanolone group at 60 hours 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 HAMD-17 <7, measured at 60 hours, was seen in 7 of 10 of the brexanolone group compared with 1 of 11 in the placebo group. Similarly, at 30 days, 7 of 10 of the brexanolone IV group and 2 of 11 in the placebo group were in remission. Brexanolone IV was found to be generally well-tolerated. There were no deaths, serious adverse events or discontinuations due to adverse events in the Phase 2 clinical trial. The most common side effects in the brexanolone group of the Phase 2 clinical trial were dizziness and somnolence.

SAGE-217

Overview

Our next most advanced product candidate is SAGE-217, an oral compound that is currently in Phase 3 clinical development in PPD and MDD. SAGE-217 is a novel neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. We are also exploring SAGE-217 in other indications, including bipolar depression and sleep disorders.

Depression Program

SAGE-217 is currently in Phase 3 clinical development as a treatment for the potentially debilitating mood disorders: MDD and PPD. The FDA has granted SAGE-217 Breakthrough Therapy designation and Fast Track designation in the treatment of MDD.

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 another medical condition 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.

To date we have completed two pivotal clinical trials of SAGE-217, one in MDD and one in PPD. In December 2017, we announced the top-line results of our double-blind, placebo-controlled pivotal Phase 2 clinical trial of SAGE-217 in MDD, which included 89 adult patients with moderate to severe MDD. In the trial, treatment for 14 days with SAGE-217 was associated with a statistically significant mean reduction from baseline in the HAMD-17 total score at Day 15 (the time of the primary endpoint) of 17.6 points for the SAGE-217 group, compared to 10.7 for the placebo group ($p<0.0001$). Statistically significant mean improvements in the HAMD-17 score compared to placebo were observed by the morning following the first dose through Week 4, and the effects of SAGE-217 remained numerically greater than placebo through the end of follow-up at Week 6, but were not statistically significant compared to placebo at Week 6. At Day 15, 64 percent of patients who received SAGE-217 achieved remission, defined as a score of 7 or less on the HAMD-17 score, compared with 23 percent of patients who received placebo ($p=0.0005$). SAGE-217 was generally well-tolerated in the trial with no serious adverse events. The overall number of reports of adverse events was similar between drug (53%) and placebo (46%). A low rate of discontinuations due to adverse events was reported. The most common adverse events in the SAGE-217 group were headache, dizziness, nausea, and somnolence.

The Phase 2 placebo-controlled trial of SAGE-217 in MDD was initiated following completion of an earlier open-label proof-of-concept clinical trial (Part A) 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, or muscle pain. The trial also examined the effect of SAGE-217 on the HAMD-17 total score, in addition to other secondary measures. Patients in the trial had a mean HAMD-17 total score of 27.2 at baseline. Data demonstrated a mean reduction from baseline in the HAMD-17 score of 19.9 points at Day 15, with 85% (11 of 13) patients showing at least a 50% reduction of their HAMD-17 and 62% (8 of 13) of patients achieving remission, as determined by a HAMD-17 ≤ 7. A statistically significant mean change from baseline was observed by Day 2 of the trial, 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).

In January 2019, we announced the results of a pivotal trial of SAGE-217 in PPD. In this placebo-controlled clinical trial of 151 women with severe PPD, SAGE-217 had a statistically significant improvement of 17.8 points in the HAMD-17 score, compared to 13.6 for placebo (primary endpoint, $p=0.0028$), with statistically significant reductions in HAMD-17 compared to placebo maintained through the end of the four-week follow-up (-19.2 vs. -15.1; $p=0.0027$). Statistically significant differences in the reduction in HAMD-17 total score of SAGE-217 versus placebo were first observed on Day 3 (-12.5 vs. -9.8; $p=0.0252$) and the effect was maintained at each timepoint through two weeks of treatment (-17.8 vs. -13.6; $p=0.0028$), the primary endpoint of the study. The effect was maintained through the four-week follow-up. Remission was achieved in 45% of patients treated with SAGE-217 for two weeks as measured by the HAMD-17 compared with 23% of patients receiving placebo ($p=0.0110$); at the end of the four-week follow-up, 53% of patients receiving SAGE-217 achieved remission compared with 30% of patients who received placebo ($p=0.0091$). After two weeks of treatment with SAGE-217, 72% of patients achieved a response (50% improvement from baseline HAMD-17 score) compared with 48% of patients who received placebo ($p=0.0049$); at the end of the four-week follow-up, 75% of patients receiving SAGE-217 achieved a response compared with 57% of patients who received placebo ($p=0.0216$). Statistically significant differences in the reduction in Montgomery-Åsberg Depression Rating Scale (MADRS) score for the SAGE-217 treatment group versus placebo were observed after two weeks of treatment (-22 vs. -18; $p=0.0180$) and the effect was maintained through the end of the four-week follow-up (-25 vs. -19; $p=0.0018$). Other secondary endpoints, including the Hamilton Anxiety Rating Scale (HAM-A) and Clinical Global Impression – Improvement (CGI-I) Scale, also showed statistically significant improvements in favor of SAGE-217 as compared to placebo. SAGE-217 was generally well-tolerated in the trial, with a safety profile consistent with that seen in earlier SAGE-217 trials. Overall reports of adverse events were similar between SAGE-217 (58%) and placebo (51%). Two subjects experienced serious adverse events, one subject in each group. The most common adverse events in the SAGE-217 treatment group were: somnolence, headache, dizziness, upper respiratory tract infection, diarrhea, and sedation.

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Our development plan for SAGE-217 is subject to ongoing discussions with the FDA. The ongoing Phase 3 clinical trials for SAGE-217 in MDD are: a placebo-controlled Phase 3 clinical trial in patients with MDD, known as the Mountain Study, in which we are studying two weeks of treatment with SAGE-217 followed by four weeks of follow-up and an ongoing open-label retreatment study, known as the Shoreline Study, evaluating initial treatment with SAGE-217, treatment-free intervals, and as needed retreatment, in patients with MDD in which patients will be followed for up to a year after treatment. Dosing in the Mountain Study commenced in December 2018, and we expect to report top-line results from this study in the fourth quarter of 2019 or the first quarter of 2020. We plan to add an open-label extension trial to the Mountain Study under a separate protocol to continue to follow patients from the Mountain Study after completion for up to six months. As part of our Phase 3 clinical development program for SAGE-217 in depression, we also plan to initiate a placebo-controlled trial to evaluate fixed interval SAGE-217 monotherapy (treatment without traditional antidepressants) for up to a year, which we believe will help us meet the expected requirements for a potential NDA filing and inclusion of maintenance dosing as part of the label, if our development efforts are successful. In addition, we are conducting a placebo-controlled polysomnography Phase 3 clinical trial of SAGE-217 in patients with MDD who have co-morbid insomnia, known as the Rainforest Study. We expect to report top-line results from the Rainforest Study and the Shoreline Study in 2020.

As part of the SAGE-217 depression program, we have also commenced dosing in a Phase 2 open-label trial evaluating four weeks of SAGE-217 treatment in a small number of patients with bipolar I/II disorder with a current major depressive episode. Bipolar depression occurs in patients with bipolar disorder. Bipolar disorder is a mood disorder in which patients experience generally distinct periods of unusually intense emotion, changes in sleep patterns, activity levels, and unusual behaviors which swing from manic episodes characterized by feeling abnormally happy or euphoric to depressive episodes characterized by feeling very sad, down, empty, or hopeless. The Phase 2 open-label trial is intended to evaluate the safety and tolerability of SAGE-217 as the primary endpoint and to study secondary endpoints, including improvements in depressive symptoms and sleep. We expect to report top-line results from this trial in the first half of 2019.

Sleep disorders

We are also exploring the potential of SAGE-217 in the treatment of sleep disorders. In January 2018, we reported positive results from a Phase 1/2, double-blind, placebo-controlled study of SAGE-217 in the treatment of 45 healthy adult volunteers using a 5-hour phase advance model of insomnia using polysomnography. SAGE-217 was administered as a single dose at either 30 or 45 mg and significantly improved sleep efficiency, or SE, to a median of 85% for 30mg ($p<0.0001$) and 88% for 45mg ($p<0.0001$) compared with a median SE of 73% for placebo. SAGE-217 also demonstrated statistically significant improvements in total sleep time and maintenance as measured by time spent awake after sleep onset. SAGE-217 was generally well-tolerated and all adverse events were mild, with no serious adverse events or adverse events leading to discontinuation.

As noted above, we initiated a placebo-controlled polysomnography trial of SAGE-217 in patients with MDD who have co-morbid insomnia in the fourth quarter of 2018. We plan to seek feedback from the FDA on potential development plans for SAGE-217 in the treatment of sleep disorders.

Shionogi Collaboration

In 2018, we entered into a collaboration with Shionogi under which we granted rights to Shionogi for the development and commercialization of SAGE-217 in Japan, Taiwan and South Korea. Shionogi has commenced Phase 1 clinical studies in Japan to evaluate the safety and tolerability of SAGE-217 in Japanese and Caucasian subjects.

SAGE-324

In addition to SAGE-217, we have a portfolio of other novel compounds that target $GABA_A$ receptors. SAGE-324 is a novel neuroactive steroid that, like brexanolone and SAGE-217, targets synaptic and extrasynaptic $GABA_A$ receptors.

We are considering developing SAGE-324 for a number of neurological conditions, including essential tremor and certain epileptiform disorders. Results from a recently completed Phase 1 single ascending dose clinical trial of SAGE-324 demonstrated that the profile of SAGE-324 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. SAGE-324 demonstrated clear target engagement in the brain using pharmaco-EEG (b-band

power) as a functional biomarker. SAGE-324 was generally well-tolerated with no serious adverse events and with a safety profile consistent with $GABA_A$ positive allosteric modulation. A Phase 1 multiple ascending dose clinical trial of SAGE-324 is ongoing. We also recently initiated a Phase 1 clinical trial to determine the safety, tolerability and pharmacokinetics of SAGE-324 in a small number of patients with essential tremor. We expect to report top-line results from the Phase 1 multiple ascending dose clinical trial and the Phase 1 essential tremor clinical trial of SAGE-324 in the second half of 2019.

Our portfolio also includes SAGE-689, a novel $GABA_A$ receptor positive allosteric modulator, with which we have conducted non-clinical studies to date, and other compounds at earlier stages of development with a focus on both acute and chronic CNS disorders.

SAGE-718

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 which we are exploring in certain cognition-related disorders impacted by NMDA receptor dysfunction, currently in Phase 1 development. Indications involving NMDA receptor hypofunction include certain types, aspects or subpopulations of a number of diseases such as depression, Huntington's disease, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, and neuropathic pain. We completed a Phase 1 single ascending dose trial of SAGE-718 in 2017 and a Phase 1 multiple ascending dose trial in 2018. The primary objective of these trials was to assess the safety, tolerability, and pharmacokinetics of SAGE-718 in healthy volunteers. Results from these Phase 1 clinical trials of SAGE-718 demonstrated that the profile of SAGE-718 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. SAGE-718 was generally well-tolerated with no serious adverse events reported. We are continuing our SAGE-718 Phase 1 clinical program with target engagement biomarker studies in healthy volunteers, focused on electrophysiology and imaging, which are ongoing and for which we expect to report results in the first half of 2019. We also recently initiated a Phase 1 clinical trial to determine the safety, tolerability and pharmacokinetics of SAGE-718 in a small number of patients with early manifest Huntington's disease. We expect to report top-line results from this trial in the second half of 2019.

Further Exploration 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. Our earlier stage efforts include $GABA_A$ receptor modulator compounds and programs such as SAGE-105 and our ST-320 and ST-210 programs, and additional compounds targeting the NMDA receptor such as SAGE-904, another positive allosteric modulator of the NMDA receptor. IND-enabling studies of SAGE-904 are ongoing. 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, and movement among others. We believe that we may 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 may also provide us, in the future, with the option, if we choose, to potentially partner certain assets with third parties who possess the development and commercialization capabilities to pursue these programs.

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Manufacturing and Supply

We neither own nor operate, and currently have no plans to own or operate, any manufacturing facilities. We currently source all of our clinical and non-clinical material supply through third party contract manufacturing organizations, or CMOs. We have also purchased the existing inventory of our proprietary formulation of brexanolone for future commercial sale, if approved, from CMOs, and intend to buy all of our future commercial supplies from CMOs if our product candidates are approved.

We have completed validation batches and are prepared for commercial supply at the launch of our proprietary formulation of brexanolone, if our NDA is approved. We have a long-term supply agreement in place with our contract manufacturer with respect to brexanolone drug substance. We have an established relationship under which a CMO manufactures drug product for our proprietary formulation of brexanolone on a purchase order basis under master service and quality agreements. We do not currently have an arrangement in place for either long-term supply of brexanolone drug product or for redundant supply of brexanolone drug product or bulk drug substance. We intend to put a long-term supply agreement in place for commercial manufacturing of brexanolone drug product in the near term, and we have an inventory of brexanolone drug product and drug substance in place to help mitigate any potential supply risks. All commercial supplies are certified by our CMOs to have been manufactured under current Good Manufacturing Practices, or cGMP.

We have established relationships with several CMOs under which the CMOs manufacture clinical and non-clinical supplies of the active pharmaceutical ingredient, or API, as well as drug product, for SAGE-217, SAGE-324, and SAGE-718 on a purchase order basis. All clinical supplies are certified by our CMOs to have been manufactured under cGMP. Starting materials and key intermediates to support the production of these candidates are manufactured by other CMOs. We do not currently have arrangements in place for either long-term supply or redundant supply of bulk drug substance or drug product for SAGE-217, SAGE-324, and SAGE-718. Our CMOs manufacture such product candidates on a purchase order basis under master service and quality agreements. We intend to put a long-term supply agreement in place at the appropriate time for drug substance and drug product for each product candidate, if development continues. We plan 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 continue to refine and scale up the manufacturing process for SAGE-217 to supply our Phase 3 clinical trials. We also intend to improve the manufacturing process for our other product candidates and manufacture clinical supplies as development progresses. We believe we currently have sufficient SAGE-217 drug substance on hand for our ongoing Phase 3 clinical trials.

Brexanolone, SAGE-217, SAGE-324 and SAGE-718 are small molecules isolated as stable crystalline solids. We believe the syntheses of brexanolone, SAGE-217, SAGE-324 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. We expect to continue to identify and develop drug candidates that are amenable to cost-effective manufacturing at contract manufacturing facilities.

Sales and Marketing

We have completed the buildout of our commercial infrastructure to support an anticipated commercial launch of ZULRESSO for the treatment of PPD in the U.S., including building a nationwide sales team, marketing and market access capabilities, and a patient support team which is located in Raleigh, North Carolina. Our ability to launch ZULRESSO in the U.S., and the timing of any such launch, are dependent on obtaining FDA approval on our expected timeline. In November 2018, the FDA extended the previously disclosed December 19, 2018 PDUFA goal date for a decision on our NDA for ZULRESSO by a period of three months to March 19, 2019. The timing of the launch of ZULRESSO in the U.S., if approved, is also dependent on the timing of anticipated scheduling of

brexanolone as a controlled substance by the DEA, which we expect to be completed 90 days after FDA approval. We anticipate that ZULRESSO, if approved, will launch in the U.S. in June 2019. As part of our ongoing launch readiness efforts in the U.S., we continue to build the systems, processes, policies, relationships and materials necessary for launch of ZULRESSO in the U.S. in PPD.

If approved, the settings for administration for ZULRESSO will be limited to healthcare facilities that have been certified under a proposed REMS program under the supervision of qualified staff to mitigate the potential for harm associated with the risk of excessive sedation and loss of consciousness during administration of ZULRESSO. As part of the proposed REMS, patients who are prescribed ZULRESSO will be required to enroll in a patient registry to allow us to compile additional information to further our understanding of the risk of a loss of consciousness during administration and management of the risk.

We believe that we can successfully launch and commercialize ZULRESSO in PPD on our own in the U.S., if the product is approved, using a targeted sales force. If the NDA for ZULRESSO in the treatment of PPD is approved by the FDA, we anticipate deploying a field sales force of key account managers calling on hospitals and specialty representatives calling on healthcare professionals who treat PPD. We expect to focus our future sales and marketing efforts, if ZULRESSO is approved for PPD, on obstetricians-gynecologists; psychiatrists; select primary care physicians and pediatricians who are likely to see women shortly after childbirth; and hospitals and other clinics capable of being certified under our REMS program. As we prepare for a potential launch, we continue to engage in permitted discussions with payors, pharmacy and therapeutic committees and formulary committees. We expect to establish a price for ZULRESSO within the range of $20,000 to $35,000 for the effective average list price per course of therapy. Commercial activities, if the NDA is approved, will focus on executing across key pillars of our go-to-market strategy by enabling Centers of Excellence under the REMS while identifying patient access and reimbursement pathways to support the experience of women with PPD who are treated with ZULRESSO. If approved as a treatment for PPD, ZULRESSO would be administered as a one-time treatment intravenously for 60 hours. Given the mode of administration, the nature of the REMS and the limitation on the administration of ZULRESSO to a healthcare facility setting certified under the REMS, we expect that use of ZULRESSO, if approved for marketing and sale in the U.S., will at least initially be focused primarily on women with more severe symptoms of PPD, which we estimate is about 20 to 30% of women diagnosed with PPD.

In addition to our efforts in the U.S., we are refining our market assessments with respect to our product candidates in the EU. We also plan to continue to evaluate market opportunities for our product candidates in other global markets. In June 2018, we entered into a collaboration agreement with Shionogi under which we granted to Shionogi rights to develop and commercialize SAGE-217 in Japan, Taiwan and South Korea. We may decide to establish agreements or alliances with one or more other pharmaceutical company collaborators or distributors to develop and commercialize one or more of our products candidates, if approved, particularly in certain territories outside the United States where we do not believe it makes business or strategic 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, 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 related to our proprietary formulation of brexanolone, and a collaboration agreement related to SAGE-217, which are described below. We have not entered into any license agreements with respect to our other clinical-stage product candidates.

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 brexanolone 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 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 brexanolone; 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 brexanolone; 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. 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 brexanolone 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. Under the supply agreement, we are required to purchase all of our requirements for Captisol with respect to brexanolone 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 investigational new drug, or 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 status epilepticus, or SE, essential tremor and/or 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 PPD. We are required to 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.

Collaboration Agreement with Shionogi & Co., Ltd.

In June 2018, we entered into a collaboration agreement with Shionogi. Pursuant to this agreement, Shionogi will be responsible for all clinical development, regulatory filings and commercialization of SAGE-217 for the treatment of MDD and potentially other indications in Japan, Taiwan and South Korea. Shionogi made an upfront payment of $90.0 million in 2018, and we will be eligible to receive additional payments of up to $485.0 million if certain regulatory and commercial milestones are achieved by Shionogi.

Under the terms of the agreement, the potential future milestone payments include up to $70.0 million for the achievement of specified regulatory milestones, up to $30.0 million for the achievement of specified commercialization milestones, and up to $385.0 million for the achievement of specified net sales milestones. We will receive tiered royalties on sales of SAGE-217 in Japan, Taiwan and South Korea, if development efforts are successful, with tiers averaging in the low to mid-twenty percent range, subject to other terms of the agreement. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, we may not receive any additional milestone payments or any royalty payments from Shionogi.

Shionogi has also granted us certain rights to co-promote SAGE-217 in Japan. We maintain exclusive rights to develop and commercialize SAGE-217 outside of Japan, Taiwan and South Korea. The upfront cash payment and any payments for milestones and royalties we receive from Shionogi are non-refundable, non-creditable and not subject to set-off.

The agreement with Shionogi will terminate on a licensed product-by-licensed product basis on the date on which the royalty term has expired in each country in Shionogi's territory for such licensed product and will ultimately expire upon the expiration of the last-to-expire royalty term. At any time following the second anniversary date of the agreement, Shionogi may remove South Korea or Taiwan from the covered territories, for any reason or no reason upon 180 days' prior written notice. Shionogi may terminate the agreement in its entirety for any reason or no reason upon 180 days' prior written notice, provided that such termination shall not be effective prior to the second anniversary of the agreement. Shionogi may also terminate the agreement in the event of a serious adverse event or a clinical failure upon 60 days' written notice to us. Either party may terminate this agreement early in the event of an uncured material breach within 180 days' after notice is delivered to the other party.

Intellectual Property

We strive to protect the proprietary know-how and 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. To protect our rights to our proprietary know-how and technology, we require all employees, as well as our consultants and contract research organization, or CROs, when feasible, to enter into agreements that require disclosure and assignment to us of ideas, developments, discoveries and inventions made by these employees, consultants, and CROs in the course of their service to us.

We plan to continue to expand our intellectual property estate by filing patent applications directed to compositions, methods of use, treatment and patient selection, 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.

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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 be enforceable or 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 hold issued patents and pending patent applications in the United States, and in certain foreign countries. Our intellectual property holdings include and are not limited to:

- One allowed United States patent application, exclusively licensed to us, covering a method of using our proprietary brexanolone formulation to treat postpartum depression, and United States and foreign patent applications covering our proprietary formulation of brexanolone and uses of the formulation to treat various CNS disorders, including postpartum depression.
- United States and foreign patent applications covering certain aspects of brexanolone, including courses of treatment, dosage regimens, and methods for manufacturing brexanolone IV.
- One issued United States patent covering the composition of matter of SAGE-217, one issued United States patent covering methods of using SAGE-217, and one granted European patent covering the composition of matter of SAGE-217, each of which expires in April 2034, subject to any potential extensions; and pending United States and foreign patent applications covering SAGE-217, uses of SAGE-217 to treat various CNS disorders, and solid forms of SAGE-217.
- United States and foreign patent applications covering SAGE-324, SAGE-105, and many other modulators of the $GABA_A$ receptor and uses of these compounds to treat various CNS disorders.
- Two issued United States patents covering composition of matter and method of use of SAGE-689 which expire in December 2033. United States and foreign patent applications covering SAGE-689 and uses of SAGE-689 to treat various CNS disorders. These patents and patent applications are co-owned with Washington University, and Sage has an exclusive license to Washington University’s rights in these patents and patent applications.
- United States and foreign patents and patent applications covering SAGE-718 and many other modulators of the NMDA receptor, and uses of these compounds to treat various CNS disorders.

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 also 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.

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.

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, including NMDA receptor antagonists or partial antagonists such as esketamine, rapastinel, and apimostinel and the opioid receptor antagonist combination product, buprenorphine/samidorphan.

The treatment plan for bipolar depression commonly consists of a combination of medication and psychotherapy. Medications used to treat bipolar depression include mood stabilizers, atypical antipsychotics and antidepressants.

There are a number of pharmacological treatments and nonpharmacological treatments for sleep disorders depending on the cause and nature of the sleep disruption.

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/pharmacovigilance, safety and periodic reporting, marketing and export and import of drug products. Generally, before a new drug can be marketed in a given jurisdiction, considerable data demonstrating its quality, safety and efficacy must be obtained and/or generated, organized into a format specific to each regulatory authority, submitted for review and the drug must be approved by the relevant regulatory authority or authorities.

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, and local 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 on a clinical investigation, warning or untitled 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 penalties or criminal prosecution. 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 requires substantial time, effort and financial resources and 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 representing 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 collectively referred to as good clinical practice, or GCP, to establish the safety and efficacy of the proposed drug for each proposed indication;
- Submission to the FDA of an NDA for marketing approval of a new drug;
- A determination by the FDA within 60 days of its receipt of an NDA to accept and file the NDA for review;

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- Satisfactory completion of a potential 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
- Payment of applicable user fees 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 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 laws and regulations, including, for animal studies, the Animal Welfare Act and GLP. 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 condition being studied under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials must be conducted in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any given 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 GCP, including review and approval by an independent ethics committee and compliance with informed consent principles, and FDA is able to validate the data from the study through an onsite inspection if deemed necessary.

Clinical Trials

Clinical trials are generally conducted in three 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 and labeling. Phase 3 clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended for drugs intended for chronic dosing 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, increased rates of serious suspected adverse events, or findings from other studies or 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, and may suspend a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. 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, certain NDAs or supplements 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 Best Pharmaceuticals for Children Act, or BPCA, the FDA may also issue a Written Request asking a sponsor to conduct pediatric studies related to a particular active moiety; if the sponsor agrees and meets certain requirements, the sponsor may be eligible to receive additional marketing exclusivity for its drug product containing such active moiety.

Under the PDUFA, as amended, each NDA must be accompanied by a user fee, unless subject to a waiver. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through September 30, 2019, the user fee for an application requiring clinical data, such as an NDA, is approximately $2.6 million. PDUFA also imposes an annual prescription drug program fee for human drugs of approximately $0.3 million. 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-designated 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 aims to complete its initial review of an NDA and respond to the applicant within 10 months from the filing date for a standard NDA and, and within 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. Before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements and integrity of the data submitted in the NDA. 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. For example, the advisory committee may recommend or the FDA may determine that a REMS program is necessary to ensure safe use of the product. 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 additional 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 patient populations 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 may involve clinical trials designed to further assess a drug's safety and/or 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 the FDA determines that 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. For example, the FDA has proposed a REMS for ZULRESSO to mitigate the potential for harm associated with the risk of excessive sedation and loss of consciousness during the ZULRESSO infusion. If approved, as part of the REMS, administration of ZULRESSO will be limited to certified healthcare facilities that have been certified under a REMS program under the supervision of qualified staff, and patients who are prescribed ZULRESSO will be required to enroll in a patient registry to allow us to compile additional information to further our understanding of the risk of excessive sedation and loss of consciousness during administration and management of the risk. Any limitations on approval, marketing or use for any of our products could restrict the commercial promotion, distribution, prescription or dispensing of those 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 for the drug for the proposed rare disease or condition. After the FDA grants orphan drug designation, the common name of the therapeutic agent and its designated orphan use are disclosed publicly by the FDA. Orphan product designation does not, by itself, 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 sponsors' 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. Orphan exclusivity operates independently from other regulatory exclusivities and other protection against generic competition, including patents that we hold for our products. A sponsor of a product application that has received an orphan drug designation may also be granted tax incentives for clinical research undertaken to support the application. In addition, the FDA may coordinate with the sponsor on research study design for an orphan drug and may exercise its discretion to grant marketing approval on the basis of more limited product safety and efficacy data than would ordinarily be required, based on the limited size of the applicable patient population.

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. The FDA can revoke a product's orphan drug exclusivity under certain circumstances, including when the holder of the approved orphan drug application is unable to assure the availability of sufficient quantities of the drug to meet patient needs. Orphan drug status in the EU has similar, but not identical, benefits.

Expedited Development and Review Programs

The FDA has several programs that are intended to expedite or facilitate the process for reviewing new drugs that are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition and provides meaningful therapeutic benefit over existing treatments. Fast Track designation and Breakthrough Therapy designation are two of these programs and apply 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 development of the product and may request the FDA to designate the drug as a Breakthrough Therapy based on preliminary clinical evidence which meet the criteria outlined in the FDA's programs. Under the Fast Track or Breakthrough Therapy expedited programs, 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 or Breakthrough Therapy 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 treats a serious condition and offers a significant improvement in the safety and effectiveness of treatment, diagnosis or prevention compared to marketed products. Significant improvement may be shown by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. 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, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months from the date of the NDA filing.

A product may also be eligible for accelerated approval if the product is intended to treat a serious or life-threatening illness and provides meaningful therapeutic benefit over existing treatments. Accelerated approval for a product means that it 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.

Fast Track designation, priority review, accelerated approval and Breakthrough Therapy 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. The FDA, if it learns of new information, may also request that the sponsor amend the initial PSP.

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, and the Drug Supply Chain Security Act, or DSCSA.

FDA regulations also require that approved 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, administrative enforcement, warning or untitled letters from the FDA, mandated corrective advertising or communications with doctors, and civil penalties or criminal prosecution, 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 Department of Health and Human Services; the United States Department of Justice; the DEA; 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, a drug product approved by the FDA may also be subject to regulation under the Controlled Substances Act (CSA) as a controlled substance. The CSA is administered by the DEA and establishes, among other things, certain registration, security, recordkeeping, reporting, import, export and other requirements for controlled substances. The CSA classifies controlled substances into five schedules: Schedule I, II, III, IV or V. FDA approved pharmaceutical products may be listed in Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances. An approved drug product or drug candidate that has not yet been approved by the FDA may be subject to scheduling as a controlled substance under the CSA, depending on the drug's potential for abuse. For a drug approved by the FDA and determined to require control under the CSA, the CSA requires the DEA to issue an interim final order scheduling the drug within 90 days after the FDA approves the drug and the DEA receives a scientific and medical evaluation and scheduling recommendation from the Department of Health and Human Services, after it has been completed by FDA. We expect FDA to recommend scheduling of brexanolone as a controlled substance, if approved.

In the United States, arrangements and interactions with health care professionals, third-party payors, patients and others will expose us to broadly applicable anti-fraud and abuse, anti-kickback, false claims and other health care laws and regulations. These broadly applicable laws and regulations may constrain the business or financial arrangements or relationships through which we sell, market and distribute our products, if and when we obtain marketing approval. In the U.S., federal and state health care laws and regulations that may affect our operations 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 an individual or purchase, lease or order, or the arranging for or recommending the purchase or order, of a particular item or service, for which payment may be made in whole or in part under a federal healthcare program, such as Medicare or Medicaid. This statute has been interpreted to apply to arrangements between pharmaceutical companies on one hand and prescribers, patients, purchasers and formulary managers on the other. Liability under the Anti-Kickback Statute may be established without proving actual knowledge of the statute or specific intent to violate it. In addition, 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 federal civil False Claims Act. Although there are a number of statutory exemptions and regulatory safe harbors to the federal Anti-Kickback Statute protecting certain common business arrangements and activities from prosecution or regulatory sanctions, the exemptions and safe harbors are drawn narrowly. Practices that involve remuneration to those who prescribe, purchase, or recommend pharmaceutical and biological products, including

certain discounts, or engaging such individuals as consultants, advisors, or speakers, may be subject to scrutiny if they do not fit squarely within an exemption or safe harbor. Our practices may not in all cases meet all of the criteria for safe harbor protection from anti-kickback liability. Moreover, there are no safe harbors for many common practices, such as educational and research grants, charitable donations, product support and patient assistance. Violations of this law are punishable by up to five years in prison, criminal fines, damages, administrative civil money penalties, and exclusion from participation in federal healthcare programs.

- The federal civil False Claims Act, which prohibits anyone from, among other things, knowingly presenting, or causing to be presented claims for payment of government funds 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 or knowingly and improperly avoiding, decreasing or concealing an obligation to pay money to the federal government. Actions under the False Claims Act may be brought by the federal government or as a qui tam action by a private individual in the name of the government. Many pharmaceutical manufacturers have been investigated and have reached substantial financial settlements with the federal government under the civil False Claims Act for a variety of alleged improper activities. 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 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 may include three times the actual damages sustained by the government, plus significant civil penalties for each separate false or fraudulent claim, and the potential for exclusion from participation in federal healthcare programs.

- Numerous federal and state laws, including state security breach notification laws, state health information privacy laws, and federal and state consumer protection laws, govern the collection, use, and disclosure and protection of health-related and other personal information. Failure to comply with these laws and regulations could result in government enforcement actions and create liability, private litigation, or adverse publicity. In addition, we may obtain health information from third parties, such as hospitals, healthcare professionals, and research institutions from which we or our collaborators obtain patient health information, that are subject to privacy and security requirements under the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, or HIPAA. Although we are not directly subject to the HIPAA information privacy and security provisions – other than with respect to providing certain employee benefits – we could potentially be subject to criminal penalties if we or our agents knowingly obtain or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA. In addition, HIPAA does not replace federal, state, or other laws that may grant individuals even greater privacy protections.

- The HIPAA fraud provisions, which impose criminal and civil liability for knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors, and prohibit knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement or representation, or making or using any false writing or document knowing the same to contain any materially false fictitious or fraudulent statement or entry, in connection with the delivery of or payment for healthcare benefits, items or services.

- The federal Physician Payment Sunshine Act, being implemented as the Open Payments Program, which requires manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the Centers for Medicare and Medicaid Services ("CMS"), the agency that administers the Medicare and Medicaid programs, information related to direct or indirect payments and other transfers of value to physicians and teaching hospitals, as well as ownership and investment interests held in the company by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report information regarding payments and transfers of value provided to physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, and certified nurse-midwives.

- Analogous state and local laws and regulations, such as state anti-kickback and false claims laws, which may apply to items or services reimbursed under Medicaid and other state programs or, in several states, regardless of the payer. We also may become subject to other state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state laws that restrict the ability of manufacturers to offer co-pay support to patients for certain prescription drugs; state laws that require drug manufacturers to report information related to clinical trials, or information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; state laws and local ordinances that require identification or licensing of sales representatives; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Substantial resources are necessary to ensure that our business arrangements and interactions with health care professionals, third party payors, patients and others comply with applicable health care laws and regulations. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law, and if we are found to be in violation of any of these laws or any other governmental regulations, we may be subject to significant civil, criminal and administrative penalties, imprisonment, damages, fines, exclusion from government funded health care programs such as Medicare and Medicaid, or the curtailment or restructuring of our operations. Any action against us for violation of these laws or regulations, 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.

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 the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to herein as 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, if any, 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 ("testing phase"), plus the time between the submission date of an NDA and the approval of that application ("approval phase"). This patent term restoration period may be reduced by the FDA if it finds that applicant did not act with due diligence during the testing phase or the approval phase. 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, if circumstances permit, we intend to apply for restoration of patent term for one of our then owned or licensed patents, if any, 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.

Some of our products may also be entitled to certain non-patent-related data exclusivity under the FDCA. The FDCA provides a five-year period of non-patent data 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, an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA may not be submitted by another company for another drug containing 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 Orange Book 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, for new indications, dosages or strengths of an existing drug. Three-year exclusivity prevents the FDA from approving ANDAs and 505(b)(2) applications that rely on the information that served as the basis of granting three-year exclusivity. 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.

European Union Drug Development

In the European Union (EU), our future products may also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if a marketing authorization from the competent regulatory authorities in the EU 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 in a manner that is often not uniform. This has led to variations in the rules governing the conduct of clinical trials in the individual EU Member States. The EU legislator has, therefore, adopted Regulation (EU) No 536/2014, or the EU Clinical Trials Regulation. The new EU Clinical Trials Regulation, which will replace the EU Clinical Trials Directive, introduces a complete overhaul of the existing regulation of clinical trials for medicinal products in the EU, including a new coordinated procedure for authorization of clinical trials that is reminiscent of the mutual recognition procedure for marketing authorization of medicinal products, and increased obligations on sponsors to publish clinical trial results. The Clinical Trials Regulation is expected to start to apply in late 2019 or in 2020.

Clinical trials in the EU must currently be conducted in accordance with the requirements of the EU Clinical Trials Directive and applicable good clinical practice standards, as implemented into national legislation by EU Member States. Under the current regime, before a clinical trial can be initiated it must be approved in each EU Member State where there is a site at which 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.

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 or the competent authorities of the EU Member States. In most EU countries, we are also required to have an approved PIP before we can begin enrolling pediatric patients in a clinical trial.

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European Union Drug Review and Approval and Post-marketing Requirements

In the European Economic Area, or EEA, (which is comprised of 28 Member States of the EU plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after a related Marketing Authorization, or MA, has been granted. Marketing authorization for medicinal products can be obtained through several different procedures. These are through a centralized, mutual recognition procedure, decentralized procedure, or national procedure (single EU Member State). The centralized procedure allows a company to submit a single application to the European Medicines Agency (EMA). If a related positive opinion is provided by the EMA, the European Commission will grant a centralized marketing authorization that is valid in all EU Member States and three of the four European Free Trade Associations, or EFTA, countries (Iceland, Liechtenstein and Norway).

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 that is not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or for which grant of centralized marketing authorization is in the interest of patients in the EU.

The decentralized authorization procedure permits companies to file identical applications for authorization to several EU Member States simultaneously for a medicinal product that has not yet been authorized in any EU Member State. The competent authorities of a single EU Member State, the reference member state, is appointed to review the application and provide an assessment report. The competent authorities of the other EU Member States, the concerned member states, are subsequently required to grant marketing authorization for their territories on the basis of this assessment. The only exception to this is where an EU Member State considers that there are concerns of potential serious risk to public health related to authorization of the product. In these circumstances, the matter is submitted to the Heads of Medicines Agencies, or CMDh, for review. The mutual recognition procedure allows companies that have a medicinal product already authorized in one EU Member State to apply for this authorization to be recognized by the competent authorities in other EU Member States.

The maximum timeframe for the evaluation of a marketing authorization application in the EU is 210 days, not including clock stops during which applicants respond to questions from the competent authority. The initial marketing authorization granted in the EU is valid for five years. The authorization may be renewed and valid for an unlimited period unless the national competent authority or the European Commission decides on justified grounds to proceed with one additional five-year renewal period. The renewal of a marketing authorization is subject to a re-evaluation of the risk-benefit balance of the product by the national competent authorities or the EMA.

The holder of an EU marketing authorization for a medicinal product must also comply with the EU's pharmacovigilance legislation. This includes requirements to conduct pharmacovigilance, or the assessment and monitoring of the safety of medicinal products.

Various requirements apply to the manufacturing and placing on the EU market of medicinal products. Manufacture of medicinal products in the EU requires a manufacturing authorization. The manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, regulations and guidance. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and APIs, including the manufacture of APIs outside of the EU with the intention to import the APIs into the EU. Similarly, the distribution of medicinal products into and within the EU is subject to compliance with the applicable EU laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of the EU Member States. Marketing authorization holders may be subject to civil, criminal or administrative sanctions, including suspension of manufacturing authorization, in case of non-compliance with the EU or EU Member States' requirements applicable to the manufacturing of medicinal products.

In the EU, the advertising and promotion of medicinal products are subject to EU Member States' laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. Breaches of the rules governing the promotion of medicinal products in the EU could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of medicinal products to the general public and may also impose limitations on promotional activities with healthcare professionals.

European Union New Chemical Entity Exclusivity

In the European Union, innovative medicinal products that are subject to marketing authorization on the basis of a full dossier and do not fall within the scope of the concept of global marketing authorization, which prevents the same marketing authorization holder or members of the same group from obtaining separate data and market exclusivity periods for medicinal products that contain the same active substance, 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 or biosimilar application for eight years from the date of authorization of the innovative product, after which a generic or biosimilar marketing authorization application can be submitted, and the innovator's data may be referenced. However, the generic product or biosimilar products cannot be marketed in the EU for a further two years thereafter. The overall ten-year period may be extended for a further year 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, orphan drug designations are granted by the European Commission based on a scientific opinion by the EMA's Committee for Orphan Medicinal Products in relation to medicinal 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 and in relation to 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.

Orphan medicinal products are entitled to ten years of exclusivity in all EU Member States and a range of other benefits during the development and regulatory review process. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities of the product. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

In addition, grant of orphan designation by the European Commission also entitles the holder of this designation to financial incentives such as reduction of fees or fee waivers. Orphan drug designation must be requested before submitting an application for marketing authorization. Orphan drug designation does not, in itself, convey any advantage in, or shorten the duration of, the regulatory review and authorization process.

Rest of the World Regulation

For other countries outside of the U.S. and EU, 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.

Approval by a regulatory authority in one jurisdiction does not guarantee approval by comparable regulatory authorities in other jurisdictions. 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.

Coverage and Reimbursement

U.S. Healthcare Reform

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, patients, 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 products, if any, we commercialize in the future.

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 Trump 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.

The ACA is a sweeping measure intended to expand healthcare coverage within the U.S., primarily through the imposition of health insurance mandates on employers and individuals, the provision of subsidies to eligible individuals enrolled in plans offered on the health insurance exchanges, and the expansion of the Medicaid program. This law has substantially changed the way healthcare is financed by both governmental and private insurers and significantly impacts the pharmaceutical industry. Changes that may affect our business include those governing enrollment in federal healthcare programs, reimbursement changes, benefits for patients within a coverage gap in the Medicare Part D prescription drug program (commonly known as the "donut hole"), rules regarding prescription drug benefits under the health insurance exchanges, changes to the Medicaid Drug Rebate program, expansion of the Public Health Service's 340B drug pricing program, or 340B program, fraud and abuse and enforcement. These changes have impacted previously existing government healthcare programs and have resulted in the development of new programs, including Medicare payment for performance initiatives and improvements to the physician quality reporting system and feedback program.

One of the goals of 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.

Some states have elected not to expand their Medicaid programs by raising the income limit to 133% of the federal poverty level, as is permitted under the ACA. For each state that does not choose to expand its Medicaid program, there may be fewer insured patients overall, which could impact sales of our approved products that are approved and that we successfully commercialize, and our business and financial condition. Where Medicaid patients receive insurance coverage under any of the new options made available through the ACA, the possibility exists that manufacturers may be required to pay Medicaid rebates on drugs used under these circumstances, a decision that could impact manufacturer revenues. In addition, there have been delays in the implementation of key provisions of the ACA, including the excise tax on generous employer-based health insurance plans. The implications of these delays for business and financial condition, if any, are not yet clear.

Moreover, additional legislative changes to or regulatory changes under the ACA remain possible. The Trump Administration has identified repeal and replacement of the ACA as one of its priorities, and has altered the implementation of the ACA and related laws. In this regard, the U.S. Tax Cuts and Jobs Act of 2017, signed into law in December 2017, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." The nature and extent of any additional legislative changes to the ACA are uncertain at this time. In addition, in December 2018, a federal district court judge, in a challenge brought by a number of state attorneys general, found the ACA unconstitutional in its entirety because once Congress repealed the "individual mandate" provision as part of tax reform legislation enacted in late 2017, there was no longer a basis to rely on Congressional taxing authority to support enactment of the law. The court reasoned that the "individual mandate" was not severable from the rest of the ACA and found the entire Act was an unconstitutional exercise of Congressional authority. While the Trump administration and CMS have both stated that the ruling will have no immediate effect, it is unclear how this decision, subsequent appeals, if any, and other efforts to repeal and replace the ACA will impact the ACA and our business. We expect that the ACA, as currently enacted or as it may be amended, and other healthcare reform measures that may be adopted in the future, could have a material adverse effect on our industry generally and on our ability to commercialize our product candidates, if approved.

Other legislative changes relating to reimbursement have been 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 to 2027 unless additional Congressional action is taken. 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.

Pharmaceutical Pricing and 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, which are increasingly reducing reimbursements for medical products and services. 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. 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.

If we are successful in developing and gaining regulatory approval for our product candidates, we intend to participate in the Medicaid Drug Rebate Program. The Medicaid Drug Rebate Program and other governmental programs impose obligations to report pricing figures to the federal government, meaning that we would be subject to these price reporting and other compliance obligations. Other programs impose limits on the price we will be permitted to charge certain entities for our products, if any, for which we receive regulatory approval. Statutory and regulatory changes or other agency action regarding these programs and their requirements could negatively affect the coverage and reimbursement by these programs of products for which we receive regulatory approval and could negatively impact our results of operations.

The Medicaid Drug Rebate Program was established by the Omnibus Budget Reconciliation Act of 1990 and amended by the Veterans Health Care Act of 1992 as well as subsequent legislation. If we participate in the Medicaid Drug Rebate Program, we will be required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the state for our drugs under Medicaid and Medicare Part B. Those rebates will be based on pricing data reported by us on a monthly and quarterly basis to CMS, the federal agency that administers the Medicare and Medicaid programs. These data will include the average manufacturer price and, in the case of innovator products, the best price for each drug, which, in general, represents the lowest price available from the manufacturer to any entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts, and other price concessions. The ACA made significant changes to the Medicaid Drug Rebate program, and CMS issued a final regulation, which became effective on April 1, 2016, to implement the changes to the Medicaid Drug Rebate Program under the ACA. Our failure to comply with these price reporting and rebate payment options could negatively impact our financial results.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Public Health Service's 340B drug pricing discount program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B drug pricing program, which is administered by the Health Resources and Services Administration, or HRSA, requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as hospitals that serve a disproportionate share of low-income patients. The ACA expanded the list of covered entities to include certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts "orphan drugs" from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program, and in general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price calculation and discount requirement. Changes to the definition of average manufacturer price and the Medicaid Drug Rebate amount under the ACA or otherwise also could affect our 340B ceiling price calculations and negatively impact our results of operations.

HRSA issued a final regulation regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, which became effective on January 1, 2019. It is currently unclear how HRSA will apply its enforcement authority under the new regulation. HRSA also is implementing a ceiling price reporting requirement related to the 340B program during the first quarter of 2019, pursuant to which we are required to report our 340B ceiling prices to HRSA on a quarterly basis. Implementation of the civil monetary penalties regulation and the issuance of any other final regulations and guidance could affect our obligations under the 340B program in ways we cannot anticipate. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in the inpatient setting.

Federal law also requires that a company that participates in the Medicaid Drug Rebate Program report average sales price information each quarter to CMS for certain categories of drugs that are paid under the Medicare Part B

program. Manufacturers calculate the average sales price based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. CMS uses these submissions to determine payment rates for drugs under Medicare Part B. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our approved products that we successfully commercialize and the resulting Medicare payment rate, and could negatively

impact our results of operations. Also, the Medicare Part B drug payment methodology is subject to change based on potential demonstration projects undertaken by CMS or potential legislation enacted by Congress.

Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by us, governmental or regulatory agencies and the courts. The Medicaid rebate amount will be computed each quarter based on our submission to CMS of our current average manufacturer prices and best prices for the quarter. If we participate in the Medicaid Drug Rebate Program and become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for a period not to exceed 12 quarters from the quarter in which the data originally were due. Such restatements and recalculations would increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program. Any corrections to our rebate calculations could result in an overage or underage in our rebate liability for past quarters, depending on the nature of the correction. Price recalculations also may affect the ceiling price at which we are required to offer our products to certain covered entities, such as safety-net providers, under the 340B drug pricing program.

If we participate in the Medicaid Drug Rebate Program and consequently the 340B drug pricing program, we could be held liable for errors associated with our submission of pricing data. Civil monetary penalties can be applied if we are found to have made a misrepresentation in the reporting of our average sales price, or if we are found to have charged 340B covered entities more than the statutorily mandated ceiling price. In addition to retroactive rebates and the potential for 340B program refunds, if we are found to have knowingly submitted false average manufacturer price or best price information to the government, we may be liable for significant civil monetary penalties per item of false information. Our failure to submit monthly/quarterly average manufacturer price and best price data on a timely basis could result in a significant civil monetary penalty per day for each day the information is late beyond the due date. Such failure also could be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we will participate in the Medicaid program. In the event that CMS terminates our rebate agreement, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs.

CMS and the OIG have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. If we participate in the Medicaid Drug Rebate Program and consequently the 340B drug pricing program, we cannot assure you that our submissions will not be found by CMS to be incomplete or incorrect.

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by the Department of Veterans Affairs (“VA”), Department of Defense (“DoD”), Public Health Service, and Coast Guard (the “Big Four agencies”) and certain federal grantees, we will be required to participate in the VA Federal Supply Schedule (“FSS”) pricing program, established under Section 603 of the Veterans Health Care Act of 1992. Under this program, we will be obligated to make our “covered” drugs (i.e., innovator drugs and biologics) available for procurement on an FSS contract and charge a price to the Big Four agencies that is no higher than the Federal Ceiling Price (“FCP”), which is a price calculated pursuant to a statutory formula. The FCP is derived from a calculated price point called the “non-federal average manufacturer price” (“Non-FAMP”), which we will be required to calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to significant civil monetary penalties for each item of false information. The FSS contract also contains extensive disclosure and certification requirements. In addition, Section 703 of the National Defense Authorization Act for FY 2008, will require us to pay quarterly rebates to DoD on utilization of covered drugs that are dispensed through DoD’s Tricare network pharmacies to Tricare beneficiaries. The rebates are calculated as the difference between the annual Non-FAMP and FCP for the calendar year that the product was dispensed. If we overcharge the government in connection with the FSS contract or Tricare Retail Pharmacy Rebate Program, whether due to a misstated FCP or otherwise, we will be required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False Claims Act and other laws and regulations. Unexpected refunds to the

government, and any response to government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

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 EU Member States have the power 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. An EU 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.

In various EU Member States, we expect to be subject to continuous cost-cutting measures, such as lower maximum prices, lower or lack of reimbursement coverage and incentives to use cheaper, usually generic, products as an alternative. Health Technology Assessment, or HTA, of medicinal products is becoming an increasingly common part of the pricing and reimbursement procedures in some EU Member States, including countries representing major markets. The HTA process, which is governed by the national laws of these countries, is the procedure according to which the assessment of the public health impact, therapeutic impact and the economic and societal impact of use of a given medicinal product in the national healthcare systems of the individual country is conducted. The outcome of HTA regarding specific medicinal products will often influence the pricing and reimbursement status granted to these medicinal products by the competent authorities of individual EU Member States. On January 31, 2018, the European Commission adopted a proposal for a regulation on health technologies assessment. This legislative proposal is intended to boost cooperation among EU Member States in assessing health technologies, including new medicinal products, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The proposal provides that EU Member States will be able to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU Member States will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technology, and making decisions on pricing and reimbursement. The European Commission has stated that the role of the draft HTA regulation is not to influence pricing and reimbursement decisions in the individual EU Member States. However, this consequence cannot be excluded.

Employees

As of February 11, 2019, we employed 637 full-time employees, including 282 in research and development and 355 in general and administrative and no part-time employees. 92 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. In October 2018, we entered into the Seventh Amendment to the Lease (the “Seventh Amendment”) to increase the amount of square feet of office space that we lease in the multi-tenant building in which our corporate headquarters are located. Prior to entering the Seventh Amendment, we rented 54,943 square feet of office space in this multi-tenant building under an operating lease that was scheduled to expire on August 15, 2024. The Seventh Amendment increased the amount of leased space at this location by 3,499 square feet beginning on December 1, 2018. The lease for this additional space will expire on August 31, 2024. Additionally, the term of the existing lease has been extended from August 15, 2024 until the expiration date of the Seventh Amendment on August 31, 2024.

In May 2016, we entered into a separate lease with an original expiration date of February 28, 2022, under which, beginning on September 1, 2016, we rent 19,805 square feet of additional office space in a separate multi-tenant building in Cambridge, MA. In April 2018, we entered into the First Amendment to the lease for office space in that building. We increased the amount of square feet of office space from 19,805 square feet to 40,419 square feet, an increase of 20,614 square feet, consisting of (i) 13,481 square feet beginning on August 1, 2018, and (ii) 7,133 square feet beginning on October 1, 2018. The term for this additional space will expire on August 31, 2024. Additionally, the term of the existing lease was extended from February 28, 2022 until August 31, 2024. We have entered into other non-material leases and expect to lease additional space prior to the expiration of our leases to meet the needs of the business.

Legal Proceedings

In the ordinary course of our business we may, from time to time, be involved in lawsuits, claims, and other legal proceedings related to contracts, employment arrangements, operating activities, intellectual property or other matters. While the outcome of any such proceedings cannot be predicted with certainty, as of the date of this Annual Report on Form 10-K, we were not party to any legal proceedings or claims that we would expect to have a material adverse impact on our financial position, results of operations or cash flow.

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.

The SEC 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 titled "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 currently do not have any products approved for marketing and sale, and may never be able to successfully gain approval to market and sell any drug product. We depend heavily on the success of ZULRESSO™ (brexanolone) injection, our proprietary intravenous, or IV, formulation of brexanolone in the U.S. for which we have submitted a new drug application, or NDA, with the FDA seeking approval to market ZULRESSO as a treatment for postpartum depression, or PPD. We cannot be certain that the FDA will approve our NDA for ZULRESSO within the expected timeframes, or at all, or that we will file for or receive regulatory approval in any other region or country. Even if ZULRESSO is approved for marketing and sale in the U.S., there is no assurance that our commercialization efforts in the U.S. will be successful or that we will be able to generate revenues or profits at the levels or on the timing we expect or at levels or on the timing necessary to support our goals.

We currently do not have any products approved for marketing and sale, and may never be able to successfully gain approval to market and sell any drug product.

Our business currently depends heavily on our ability to gain approval of ZULRESSO in the U.S. as a treatment for PPD. We submitted an NDA to the FDA seeking such approval in April 2018, and the NDA is currently under review. On November 2, 2018, the Psychopharmacologic Drugs Advisory Committee, or PDAC, and Drug Safety and Risk Management, or DSaRM, Advisory Committee of the FDA jointly voted, by a vote of 17 to 1, that our data support a favorable benefit/risk profile for ZULRESSO in the treatment of PPD when administered by qualified staff in a healthcare setting certified under a Risk Evaluation and Mitigation Strategies, or REMS, program. The recommendations of PDAC and the DSaRM Advisory Committee are not binding on the FDA. The FDA may not agree with some or all of the Advisory Committees' recommendations. The FDA may determine that the clinical and non-clinical data we have generated to date are not sufficient to gain regulatory approval to commercialize ZULRESSO as a treatment for PPD in the U.S., and may seek additional trials or data in order for us to obtain approval. Similarly, the FDA may find fault with the data generated at one of our clinical sites or with the activities of our trial monitor or may disagree with how we conducted our trials or our analyses of the trial results. The FDA may also identify deficiencies or other issues with our manufacturing or quality systems or processes. Any such findings or issues could require additional data or analyses or the need for changes to our systems or processes that could delay or prevent us from gaining approval of ZULRESSO in the U.S. Even if the FDA decides to grant approval of ZULRESSO in the treatment of PPD, the FDA may impose the limitations, conditions and restrictions on any such approval that were discussed at the joint meeting of the Advisory Committees or that are different from or in addition to the limitations, conditions and restrictions discussed by the Advisory Committees.

Even if we gain approval of ZULRESSO, we may never be able to successfully commercialize the product or meet our expectations with respect to revenues or profits. We have never marketed, sold or distributed for commercial use

any pharmaceutical product. We continue to build the infrastructure, systems, processes, policies, relationships and materials necessary for launch of ZULRESSO in the U.S. in PPD. If approved, administration of ZULRESSO will be limited to healthcare facilities that are trained and certified under a REMS program under the supervision of qualified staff to mitigate the potential for harm associated with the risk of excessive sedation and loss of consciousness during administration of ZULRESSO. We continue to work with the FDA on the details of the REMS program and cannot be certain what other restrictions, limitations or conditions the FDA may require as part of the REMS program. As part of the proposed REMS program, patients receiving ZULRESSO will be required to enroll in a registry to allow us to gather

information to help further characterize the risk of excessive sedation and loss of consciousness during administration and management of the risk. Implementing these requirements and finding and certifying sites of care for administration of ZULRESSO will be challenging and complex and may take time depending on the type of facility. Certain healthcare facilities may not have the infrastructure to support administration of ZULRESSO or to implement the REMS program or the registry, or may not be willing to do so as a result of the limitations, restrictions and other requirements related to administration of ZULRESSO or the REMS or for other reasons.

Similarly, women with PPD who need treatment may find it too onerous to undergo an infusion or to be treated at a certified healthcare facility or to be enrolled in the registry or may be concerned about the risk of excessive sedation and loss of consciousness. Given the mode of administration, the nature of the REMS and the limitation on the administration of ZULRESSO to a healthcare facility setting certified under the REMS, we expect that use of ZULRESSO, if approved for marketing and sale in the U.S., will, at least initially, be focused primarily on women with more severe symptoms of PPD. We estimate that greater than 400,000 women in the U.S. experience PPD symptoms each year, of whom approximately 50% are formally diagnosed. We estimate that about 20 to 30% of women diagnosed with PPD experience severe symptoms. If we receive regulatory approval to market or sell ZULRESSO, but are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, or sufficient, accessible and acceptable REMS certified healthcare facilities for administration of ZULRESSO, or if we do not achieve a sufficient level of market acceptance, or if we are unable to do any of the foregoing in a timely manner and on commercially reasonable terms, our business, results of operations, financial condition and prospects will be materially adversely affected. There is no guarantee that we will be successful in our launch or commercialization efforts with respect to ZULRESSO. We may encounter issues, delays or other challenges in launching or commercializing ZULRESSO and generating revenues, if approved. For example, our results may be negatively impacted if we have not adequately sized our field teams or our physician segmentation and targeting strategy is inadequate or if we encounter deficiencies or inefficiencies in our infrastructure or processes. We may encounter unexpected limitations in the scope, breadth, availability or amount of reimbursement covering ZULRESSO, if approved, or other limitations or issues related to the price. We may face other issues related to market acceptance and use of ZULRESSO, if approved, including: challenges related to the IV mode of administration of ZULRESSO or the risk/benefit profile; limitations in the number, accessibility and acceptability of settings for administration due to the requirement for a REMS certified healthcare facility or the other requirements of the REMS program; financial burdens of treatment for the patient or site of care; or competition from lower cost anti-depressants. Any of these issues could impair our ability to successfully commercialize the product or to generate substantial revenues or profits or to meet our expectations with respect to the amount or timing of revenues or profits.

Our future business prospects also depend heavily on our ability to successfully develop and gain regulatory approval of our other current product candidates beyond ZULRESSO, of which SAGE-217 is in Phase 3 clinical development for major depressive disorder, or MDD, and PPD, and is being explored in other indications; and other product candidates are at earlier stages. We cannot be certain that we will be able to complete ongoing clinical trials or initiate future planned clinical trials, or to announce results of such trials, with respect to SAGE-217 or any of our other product candidates on the time-lines we expect or at all or that the design or results of our development programs will be sufficient to file for and gain regulatory approval. 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.

Drug development is a long, expensive and uncertain process, involving a high degree of risk. Our business depends heavily on our ability to complete clinical development and non-clinical studies of SAGE-217 and our other current product candidates, and to obtain regulatory approval of 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. We may not be able to demonstrate the efficacy and safety of SAGE-217 or any of our other current product

candidates or any future product candidate at each stage of clinical development or we may encounter issues with any non-clinical studies required for regulatory submissions. 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 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. For example, the FDA may ultimately decide that the design, number and type of trials, number of patients studied or results of our planned clinical trials for SAGE-217 even if positive are not sufficient

for regulatory approval in MDD, PPD or any other indication, or do not support episodic treatment of MDD, which is the current focus of our development plan, or may ultimately require a development plan that supports chronic treatment based on results from clinical trials. We may not be able to meet the requirements for non-clinical data or clinical data needed to advance such a development plan. Changes in formulation, or the need to refine or scale-up the manufacturing process, for our product candidates could also delay development or require us to conduct additional clinical trials or non-clinical studies or could lead to different results than achieved with the earlier formulation or processes. We may not be able to initiate or complete our clinical trials or announce results from our clinical trials on the time-lines we expect. We may experience slower than expected enrollment and randomization of patients in our clinical trials, particularly in clinical trials where an in-patient stay or frequent site visits are required or where the patient population is small or where there are existing therapies. These types of delays can lead to delays in completion of a trial and announcement of results. 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.

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 FDA regulatory approval process and will be commercialized. 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. 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 either in the U.S. or in any country outside the U.S.

Even if we gain approval of any of our other product candidates, we may never be able to successfully commercialize the product or to meet our expectations with respect to revenues or profits.

Obtaining regulatory approval to market ZULRESSO or any of our other product candidates is a complex, lengthy, expensive and uncertain process, and the FDA and regulatory authorities outside of the U.S. may delay, limit or deny approval of any of our product candidates for many reasons. Any setback or delay in obtaining regulatory approval for our product candidates or in our ability to commence marketing of our products, if approved, may have a material adverse effect on our business and prospects.

We are not permitted to market any of our product candidates in the U.S. until we receive approval of 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;
- 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 one or more of our sites conducting non-clinical studies or clinical trials which may cause the study or trial to fail;
- the FDA or regulatory authorities outside the U.S. may determine that the number, design, size, conduct, or implementation of our non-clinical studies or clinical trials are inadequate for regulatory approval or that changes in drug formulation used in our non-clinical studies or clinical trials require additional trials or studies, even if the regulatory authorities have previously reviewed and commented on the design and details of our plans;

- the FDA or regulatory or other government 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 an NDA for any of our product candidates 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, and the FDA may ultimately agree with the recommendations of the advisory committee;
- the FDA or applicable foreign regulatory authorities may approve a product candidate for which we are seeking regulatory approval for a more limited patient population than we expect or with substantial use restrictions;
- as the FDA has proposed with respect to ZULRESSO, if approved, the FDA may require development of a 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.

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. Even if we receive marketing approval for any of our product candidates, regulatory or other governmental authorities may still impose significant restrictions, including restrictions on the indicated use or marketing, or may impose ongoing requirements for potentially costly post-approval studies. For example, we expect that the FDA may impose additional post-approval obligations if ZULRESSO is approved. We may not be able to fulfill these obligations in accordance with the FDA's timelines, or at all. We also expect that the FDA will recommend controlled substances scheduling of brexanolone and may recommend scheduling with respect to any of our other product candidates. In such event, prior to a product launch, the U.S. Drug Enforcement Agency, or DEA, will need to determine the controlled substance schedule of the product, taking into account the recommendation of the FDA. The timing of the scheduling process is uncertain and may delay our ability to market any such product if it is approved.

Even if we receive marketing approval for our product candidates in the U.S., we may never seek or receive regulatory approval to market our product candidates outside of the U.S., or receive pricing and reimbursement outside the U.S. at acceptable levels. We cannot be certain that we will be able, or willing, to support the submission of a marketing authorization application, or MAA, to the EMA for ZULRESSO in PPD, or that we will decide to file an MAA with the EMA, or that any such MAA will ever be approved.

Even if we receive marketing approval for ZULRESSO or any of our other product candidates in the U.S., we may not seek, or may seek but never receive, regulatory approval to market our product candidates outside of the U.S. or in any particular country or region, including in the European Union, or EU. 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 non-clinical studies or clinical trials, additional work related to manufacturing and analytical testing on controls, 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 other countries. 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 may require additional studies and data, and can result in substantial delays in bringing products to market in such countries and such investment may not be justified from a business standpoint given the market opportunity or level of required investment. For example, we anticipate having additional discussions with the EMA to further clarify and evaluate what additional data and information would be required and what other requirements would need to be met for a possible MAA submission for brexanolone IV in PPD in the EU, and potential post-marketing clinical development obligations if we file an MAA and our application is approved. We may not find an acceptable regulatory path forward for brexanolone IV in the EU. Even if after additional feedback from the

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EMA, we decide to generate any required additional data and information and meet any other requirements to be able to file an MAA and the MAA is approved, we may have significant post-approval obligations.

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. without onerous restrictions or limitations related to pricing or any delay or other setback in obtaining such approval, would impair our ability to market our product candidates successfully or at all in such foreign markets. Any such impairment would reduce the size of our potential market or revenue potential, which could have a material adverse impact on our business, results of operations and prospects.

Any setback or delay in obtaining regulatory approval for our product candidates or in our ability to commence marketing of our products, if approved, may have a material adverse effect on our business and prospects.

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

We have received Breakthrough Therapy designation in the U.S. and PRIME designation in the EU for ZULRESSO in the treatment of PPD. We have received Breakthrough Therapy designation and Fast Track designation for SAGE-217 in the treatment of MDD. In the future, we may seek Fast Track, Breakthrough Therapy or PRIME designations for these product candidates in indications not yet covered or for our other product candidates. These designations 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 have difficulties in enrolling patients in our clinical trials which may delay or prevent development of our product candidates, and even if such product candidates are successfully developed and approved, the markets for our products may be smaller than we expect and our revenue potential and ability to achieve profitability may be materially adversely affected.

We have filed an NDA in the U.S. seeking approval of our lead product, ZULRESSO, for the treatment of women with PPD. We are developing our next generation product candidate, SAGE-217, in MDD, PPD, bipolar depression, and sleep disorders. There is no precise method of establishing the actual number of patients with any of these disorders in any geography over any time period. With respect to many of the indications in which we have developed, are developing, 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 PPD, MDD, and bipolar depression, 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 and in marketing studies which include estimates within the range that are lower than our estimates. For example, our estimates of the prevalence of PPD are higher than estimates reported in some of the published literature and results obtained from certain studies analyzing claims databases. We believe these differences may be the result of variations in analytical methodologies and possibly 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 PPD, MDD, bipolar depression, or any other indication in which we elect to pursue development of our product candidates may, however, be significantly lower than we believe. In addition, 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 product candidates may be developed for only a subset of patients with the relevant disease or disorder or our products, if approved, may be indicated or used for only a subset. For example, the IV infusion mode of administration for ZULRESSO; limitations on sites of care for administration of ZULRESSO to REMS certified healthcare facilities; the requirement for a registry as part of the REMS, and the other requirements of the REMS; and the risk of excessive sedation and loss of consciousness may limit the type of women who are prescribed ZULRESSO or who actually receive treatment, if the drug is ultimately approved, to those patients with more severe symptoms of PPD even beyond the initial launch period. In the event the number of patients with the diseases and disorders we are studying is significantly lower than we expect, we may have difficulties in enrolling patients in our clinical trials which may delay or prevent development of our product candidates. If any of our product candidates are approved and our prevalence estimates with respect to any indication or our other

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 or to meet our expectations with respect to revenues or profits.

If serious adverse events or other undesirable side effects are identified during the use of 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, our ability to gain regulatory approval or market acceptance if the product is approved.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt 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 any of our other product candidates are observed in clinical trials, emergency-use cases, investigator sponsored clinical trials, expanded access, 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. 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. Even if our product candidates are approved, any such events could limit market acceptance of our product. The occurrence of any of these events could have a material adverse effect on our business.

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 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 results of our Phase 2 placebo-controlled clinical trial of SAGE-217 in MDD may not be replicated in ongoing and planned Phase 3 clinical trials in MDD which will involve a larger number of patients. By way of example, our results in an earlier clinical trial were not replicated in our Phase 3 clinical trial of ZULRESSO in super-refractory status epilepticus. 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 to 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 or equivalent filings outside the U.S. and, consequently, the ultimate approval and commercial marketing of any of our 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:

- denial by the FDA or other regulatory authority of permission to proceed with our planned clinical trials or any other clinical trials we may initiate, or placement of 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 some cases, due to: the small size of the patient population being studied; the lack of proximity of some patients to trial sites; challenges in meeting regulatory and material requirements to commence clinical trials in countries outside the U.S.; eligibility criteria for the clinical trial; challenges associated with the nature of the clinical trial protocol; 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, any of which could delay enrollment of patients in ongoing or future clinical trials of our product candidates;
- delays in reaching or failing to reach agreement on acceptable terms with prospective contract research organizations, or 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 supplies of a product candidate or other materials necessary to conduct clinical trials, for example as a result of delays in defining, refining and implementing the manufacturing process for materials used in pivotal trials or for the manufacture of larger quantities or other delays or issues arising 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 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 or 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. We are in the process of evaluating possible alternative formulations of SAGE-689, but there is no guarantee that an alternative formulation for SAGE-689 will be sufficient to continue development. 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 development pathway, and ultimately 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, comply with applicable standards and 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;
- fail to comply with cGCP or experience other 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 and all of our clinical sites 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 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 ZULRESSO (brexanolone) injection, our proprietary IV formulation of brexanolone for commercial use, if approved for marketing and sale, or of any of our other existing or future product candidates, for use in the conduct of our clinical trials and non-clinical studies or for future commercial use, and we rely completely on third-party suppliers for both active drug substances and finished drug products.

We continue to work with our contract manufacturers to prepare for commercial supply of ZULRESSO. We will rely on our contract manufacturers for commercial supplies of active drug substance, finished drug product and packaged and labeled product with respect to ZULRESSO, if approved. We will also rely on our contract manufacturers to manufacture sufficient quantities of SAGE-217, SAGE-324, SAGE-718 and our other product candidates for ongoing and future clinical trials and non-clinical studies, and to scale our manufacturing processes for later stage clinical trials, if our development efforts at each stage are successful. 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 the relevant 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 with respect to our products. 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 significantly adversely delay or 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 have a long-term supply agreement with our contract manufacturer with respect to ZULRESSO drug substance. We do not yet have long-term supply agreements in place with our contract manufacturers with respect to ZULRESSO drug product or any of our other product candidates, and each batch of ZULRESSO drug product and each of our other product candidates is individually contracted through a purchase order governed by our master service and quality agreements. We have an inventory of ZULRESSO drug product and drug substance in place to help mitigate any potential supply risks, but there is no guarantee that this inventory will be adequate. 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.

If we are unable to establish effective sales, marketing and distribution capabilities or enter into agreements with third parties to market, sell and distribute our products, if approved, or if we are unable to achieve market acceptance for such products, our business, results of operations, financial condition and prospects will be materially adversely affected.

We have never marketed, sold or distributed for commercial use any pharmaceutical product. We are continuing to build the systems, processes, policies, relationships and materials necessary for launch of ZULRESSO in the U.S. in PPD, and to enable appropriate healthcare facilities to be certified as sites of care for administering the product. If we receive regulatory approval to market or sell ZULRESSO or any of our other product candidates, if successfully developed and approved, but 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. For example, if approved, administration of ZULRESSO will be limited to healthcare facilities that are trained and certified under a REMS program under the supervision of qualified staff. We continue to work with the FDA on the details of the REMS program and cannot be certain what other restrictions, limitations or conditions the FDA may require as part of the REMS program. If approved, patients receiving ZULRESSO will be required, as part of the REMS program, to enroll in a registry to gather information to help further characterize the risk of excessive sedation and loss of consciousness during administration of ZULRESSO and on management of the risk. Implementing these requirements and enabling sites of care will be challenging and complex and may take time depending on the site. We may encounter issues, delays or other challenges in launching or commercializing ZULRESSO or any of our other product candidates, if approved. For example, our results may be negatively impacted if we have not adequately sized our field teams or if our physician segmentation and targeting strategy is inadequate or if we encounter deficiencies or inefficiencies in our infrastructure or processes. Certain healthcare facilities may not have the infrastructure to support administration of ZULRESSO or to implement the REMS program or the registry, or may not be willing to do so as a result of the limitations, restrictions and other requirements. Similarly, women with PPD who need treatment may find it too onerous to undergo an infusion or to be treated at a healthcare facility or to be enrolled in the registry or may be concerned about the risk of excessive sedation and loss of consciousness. We may encounter unexpected limitations in the scope, breadth or amount of reimbursement covering ZULRESSO or our products, if approved, or other limitations or issues related to the price. We may never seek or be able to generate sufficient data to sufficiently satisfy the FDA so as to permit in the future administration in the home setting even with monitoring and supervision requirements. Any of these issues could impair our ability to successfully commercialize the product or to generate substantial revenues or profits or to meet our expectations with respect to the amount or timing of revenues or profits. There is no guarantee that we will be successful in our launch or commercialization efforts with respect to ZULRESSO or with respect to any other product candidate that may be approved in the future.

Even if we receive marketing approval for ZULRESSO or any of our other product candidates, our approved products may not achieve broad market acceptance or reimbursement at sufficient levels, 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, and reimbursement at sufficient levels. 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;

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- the potential and perceived advantages and limitations of our products over current treatment options or alternative treatments, including future alternative treatments, including in the case of ZULRESSO, the impact of limitations arising from the IV infusion mode of administration, restrictions on site of care to REMS certified healthcare facilities and other requirements of the REMS, and the risk of excessive sedation and loss of consciousness during administration;
- 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 deployment and 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 reimbursement at reasonable levels, 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 or may not do so on the timelines we expect. 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 products, if approved, or our product candidates during development, may cause undesirable side effects that limit the commercial profile of an approved product, or result in significant negative consequences following marketing approval, if any; or delay or prevent further development or regulatory approval of a product candidate or cause regulatory authorities to require labeling statements, such as boxed warnings.

Undesirable side effects caused by our products, if and when approved, could limit the commercial profile of such product or result in significant negative consequences following marketing approval such as a more restrictive label or other limitations or restrictions. For example, if approved, administration of ZULRESSO will be limited to healthcare settings certified under a REMS as a result of the risk of excessive sedation and loss of consciousness during administration.

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 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, certain side effects of our product candidates may only be uncovered with a significantly larger number of patients exposed to the product, and those side effects could be serious or life-threatening. 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, including as a result of inclusion in a class of drugs for a particular disease;
- 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 significant post-marketing obligations and future development and regulatory difficulties.

Even if we receive marketing approval for our product candidates, regulatory authorities may impose significant and potentially costly post-marketing obligations, including post-marketing studies, additional CMC work and additional pediatric studies. For example, we expect to have post-marketing commitments if ZULRESSO is approved by the FDA. In the event we elect, or are required, to proceed with pediatric studies of any of our product candidates in any indication, regulatory authorities may also require additional nonclinical studies or clinical trials be completed prior to commencement of such pediatric studies. Regulatory authorities may also impose significant restrictions on our products, including restrictions on indicated uses or marketing.

If the FDA approves our NDA for ZULRESSO in PPD, we expect that the FDA will recommend controlled substances scheduling in which case, prior to product launch, the DEA will need to determine the controlled substance schedule of brexanolone, taking into account the recommendation of the FDA. The scheduling process may also apply to other product candidates. 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, safety and efficacy in pediatric populations or alternate doses or dose regimens. The FDA also has the authority to require, as part of an NDA or post-approval, the submission of a REMS. For example, the FDA has proposed a REMS for ZULRESSO, if approved. 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 or in the manufacturing process, 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 manufacturer 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 that adversely affect 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 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 antidepressant medications such as selective serotonin reuptake inhibitors, or SSRIs, and serotonin and norepinephrine reuptake inhibitors, or SNRIs.

MDD patients are typically treated with a variety of antidepressant medications, including SSRIs and SNRIs. A number of companies are developing product candidates intended for the treatment of MDD, including NMDA receptor antagonists or partial antagonists such as esketamine, rapastinel, and apimostinel and the opioid receptor antagonist combination product, buprenorphine/samidorphan.

The treatment plan for bipolar depression commonly consists of a combination of medication and psychotherapy. Medications used to treat bipolar depression include mood stabilizers, atypical antipsychotics and antidepressants.

There are a number of pharmacological treatments and nonpharmacological treatments for sleep disorders, depending on the cause and nature of the sleep disruption.

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.

We have an existing collaboration, and may seek to establish additional collaborations, related to our development and commercialization of product candidates. Our existing and future collaborations, if any, may not lead to the successful development or commercialization of product candidates. If we determine that future collaborations are important to our business, and we are not able to establish future collaborations 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.

Our existing and future collaborations, if any, may not lead to the successful development and commercialization of any products. Our collaborators face both the same challenges and hurdles that we would face in the development and commercialization of product candidates if we were engaged in the activities ourselves, as well as additional challenges related to operating under a collaboration. For example, we have entered into a collaboration with Shionogi & Co., Ltd., or Shionogi, under which we granted rights to Shionogi for the development and commercialization of SAGE-217 for the treatment of MDD and potentially other indications in Japan, Taiwan and South Korea. Shionogi may not be successful in its efforts to develop SAGE-217, and we may never receive any additional milestone payments or any royalty payments from Shionogi. In addition, under most collaborations, a certain degree of control in decision-making is transferred to or shared with our collaborators in these efforts which may lead to decisions that hamper our overall development and commercialization activities. In addition, if we depend on collaborators for capabilities and funding for major product development efforts globally or in key territories then our business may be adversely affected if the collaboration terminates or if our collaborator fails to perform its obligations under the agreement. Disputes may also arise with respect to the ownership of rights to technology or products developed with collaborators, which could have an adverse effect on our ability to develop and commercialize any affected product candidate.

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 intellectual property protection or ownership of technology, which can exist if there is a challenge to such intellectual property or 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. 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. If we elect to increase our expenditures to fund development or commercialization activities on our own that we had planned to develop in collaboration with a third party, 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.

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. 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 may have a material adverse effect on our business.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs, we could be subject to additional reimbursement requirements, penalties, sanctions and fines, which could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

The Medicaid Drug Rebate Program and other governmental programs impose obligations to report pricing figures to the federal government. If we are successful in developing and gaining regulatory approval for our product candidates, we intend to participate in the Medicaid Drug Rebate Program, meaning that we will be subject to these price reporting and other compliance obligations. Other programs impose limits on the price we will be permitted to charge certain entities for our products for which we receive regulatory approval. Statutory and regulatory changes or binding guidance regarding these programs and their requirements could negatively affect the coverage and reimbursement by these programs of products for which we receive regulatory approval and could negatively impact our results of operations.

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The Medicaid Drug Rebate Program was established by the Omnibus Budget Reconciliation Act of 1990 and amended by the Veterans Health Care Act of 1992 as well as subsequent legislation. If we participate in the Medicaid Drug Rebate Program, we will be required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having federal funds being made available to the state for our drugs under Medicaid and Medicare Part B. Those rebates will be based on pricing data reported by us on a monthly and quarterly basis to the Centers for Medicare and Medicaid Services, or CMS, the federal agency that administers the Medicaid Drug Rebate Program. These data will include the average manufacturer price and, in the case of innovator products, the best price for each drug, which, in general, represents the lowest price available from the manufacturer, subject to exceptions, to any wholesaler, retailer, provider, health maintenance organization, nonprofit entity, or governmental entity in the U.S. in any pricing structure, calculated to include all sales and associated rebates, discounts, and other price concessions. Our failure to comply with these price reporting and rebate payment options could negatively impact our financial results.

Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Health Resources and Services Administration's, or HRSA, 340B drug pricing discount program in order for federal funds to be available for the manufacturer's drugs under Medicaid and Medicare Part B. The 340B drug pricing program requires participating manufacturers to agree to charge statutorily defined covered entities no more than the 340B "ceiling price" for the manufacturer's covered outpatient drugs. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Department of Health and Human Services, or HHS, as well as hospitals that serve a disproportionate share of low-income patients. The 340B ceiling price is calculated using a statutory formula, which is based on the average manufacturer price and rebate amount for the covered outpatient drug as calculated under the Medicaid Drug Rebate Program. Changes to the definition of average manufacturer price and the Medicaid Drug Rebate amount under the ACA or otherwise also could affect our 340B ceiling price calculations and negatively impact our results of operations.

The Affordable Care Act obligates HHS to update the agreement that manufacturers must sign to participate in the 340B program to obligate a manufacturer to offer the 340B price to covered entities if the manufacturer makes the drug available to any other purchaser at any price and to report to the government the ceiling prices for its drugs. HRSA, the federal agency that administers the 340B program, recently updated the agreement with participating manufacturers. The Affordable Care Act also obligates the Secretary of the HHS to create regulations and processes to improve the integrity of the 340B program. On January 5, 2017, HRSA issued a final regulation regarding the calculation of 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities. The effective date of the regulation has been delayed until July 1, 2018. Implementation of this final rule and the issuance of any other final regulations and guidance could affect our obligations under the 340B program in ways we cannot anticipate. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or would require participating manufacturers to agree to provide 340B discounted pricing on drugs used in the inpatient setting.

Federal law also requires that a company that participates in the Medicaid Drug Rebate Program report average sales price information each quarter to CMS for certain categories of drugs that are paid under the Medicare Part B program. Manufacturers calculate the average sales price based on a statutorily defined formula as well as regulations and interpretations of the statute by CMS. CMS uses these submissions to determine payment rates for drugs under Medicare Part B. Statutory or regulatory changes or CMS guidance could affect the average sales price calculations for our products and the resulting Medicare payment rate, and could negatively impact our results of operations. Also, the Medicare Part B drug payment methodology is subject to change based on potential demonstration projects undertaken by CMS or potential legislation enacted by Congress.

Pricing and rebate calculations vary among products and programs. The calculations are complex and are often subject to interpretation by us, governmental or regulatory agencies and the courts. The Medicaid rebate amount is computed each quarter based on our submission to CMS of our current average manufacturer prices and best prices for the quarter. If we participate in the Medicaid Drug Rebate Program and become aware that our reporting for a prior quarter was incorrect, or has changed as a result of recalculation of the pricing data, we are obligated to resubmit the corrected data for a period not to exceed 12 quarters from the quarter in which the data originally were due. Such restatements and recalculations would increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program. Any corrections to our rebate calculations could result in an overage or underage in our rebate liability for past quarters, depending on the nature of the correction. Price recalculations also may affect the ceiling price at which we are required to offer our products to certain covered entities, such as safety-net providers, under the 340B drug pricing program.

If we participate in the Medicaid Drug Rebate Program and consequently the 340B drug pricing program, we could be held liable for errors associated with our submission of pricing data. In addition to retroactive rebates and the potential for 340B program refunds, if we are found to have knowingly submitted false average manufacturer price or best price information to the government, we may be liable for civil monetary penalties in the amount of $181,071 per item of false information. Our failure to submit monthly/quarterly average manufacturer price and best price data on a timely basis could result in a civil monetary penalty of $18,107 per day for each day the information is late beyond the due date. Such failure also could be grounds for CMS to terminate our Medicaid drug rebate agreement, pursuant to which we participate in the Medicaid program. In the event that CMS terminates our rebate agreement, no federal payments would be available under Medicaid or Medicare Part B for our covered outpatient drugs.

CMS and the OIG have pursued manufacturers that were alleged to have failed to report these data to the government in a timely manner. Governmental agencies may also make changes in program interpretations, requirements or conditions of participation, some of which may have implications for amounts previously estimated or paid. If we participate in the Medicaid Drug Rebate Program and consequently the 340B drug pricing program, we cannot assure you that our submissions will not be found by CMS to be incomplete or incorrect.

In order to be eligible to have our products paid for with federal funds under the Medicaid and Medicare Part B programs and purchased by the Department of Veterans Affairs, or VA, Department of Defense, or DoD, Public Health Service, and Coast Guard (the “Big Four agencies”) and certain federal grantees, we will be required to participate in the VA Federal Supply Schedule, or FSS pricing program, established under Section 603 of the Veterans Health Care Act of 1992. Under this program, we will be obligated to make our covered outpatient drugs available for procurement on an FSS contract and charge a price to the Big Four agencies that is no higher than the Federal Ceiling Price, or FCP, which is a price calculated pursuant to a statutory formula. The FCP is derived from a calculated price point called the “non-federal average manufacturer price”, or Non-FAMP, which we will be required to calculate and report to the VA on a quarterly and annual basis. Pursuant to applicable law, knowing provision of false information in connection with a Non-FAMP filing can subject a manufacturer to penalties of $181,071 for each item of false information. The FSS contract also contains extensive disclosure and certification requirements.

If we participate in the Medicaid Drug Rebate Program, Section 703 of the National Defense Authorization Act for FY 2008 will require us to pay quarterly rebates to DoD on utilization of innovator products that are dispensed through DoD’s Tricare network pharmacies to Tricare beneficiaries. The rebates are calculated as the difference between the annual Non-FAMP and FCP for the calendar year that the product was dispensed. If we overcharge the government in connection with the FSS contract or Tricare Retail Pharmacy Rebate Program, whether due to a misstated FCP or otherwise, we will be required to refund the difference to the government. Failure to make necessary disclosures and/or to identify contract overcharges can result in allegations against us under the False Claims Act and other laws and regulations. Unexpected refunds to the government, and any response to government investigation or enforcement action, would be expensive and time-consuming, and could have a material adverse effect on our business, financial condition, results of operations and growth prospects.

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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 expect to 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 practices and business arrangements comply with applicable healthcare laws and regulations could be costly. It is possible that governmental authorities will conclude that our business practices and arrangements 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 practices or 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 and materially adversely affect our business and financial condition. 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.

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Inadequate funding for the FDA and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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, in compliance with applicable laws, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

We expect brexanolone will, and our other product candidates may, be regulated as controlled substances, the manufacture, use, sale, importation, exportation, prescribing and distribution of which are subject to regulation by the DEA, which may entail additional restrictions and cause delays in commercialization even if a product candidate is approved.

We expect that the FDA will determine that brexanolone should be regulated as a controlled substance. In such event or if the FDA makes that determination with respect to any other product candidates that we successfully develop, then before we can commercialize any such product candidate, 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. The DEA has established certain registration, security, recordkeeping, reporting, storage, distribution, importation, exportation, inventory, quota and other requirements administered by the DEA with respect to “controlled substances” as defined in the Controlled Substances Act of 1970, or CSA, and the implementing regulations. These requirements may be 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. As an example, Schedule IV compounds include sedative hypnotics such as benzodiazepines.

If determined to be controlled substances, 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.

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, if approved, is challenging, and may become even more challenging in the future due to, among other reasons, policies advanced by the current presidential administration or 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 or that studies the impact of our product on healthcare spending and outcomes. 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.

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 collaborations 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 ZULRESSO, 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 currently have one issued U.S. patent covering the composition of matter of SAGE-217, one issued U.S. patent covering methods of using SAGE-217, one issued U.S. patent covering the composition of matter of SAGE-689, and one issued U.S. patent covering methods of using SAGE-689. We also have granted European patents covering SAGE-217, SAGE-689 and SAGE-718. 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 be enforceable or 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 ZULRESSO only cover particular formulations and particular methods of using such formulations 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 of brexanolone 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 ZULRESSO. 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 may 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 may 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 or as 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 CROs, 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 or unenforceable, 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, CROs, outside scientific collaborators, 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 which could have a materially adverse effect on our business.

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 noncompliance 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 formalities and 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 patent applications and 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 patent protection. They may pursue and obtain their own 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 and pharmaceuticals. For example, a 2018 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.

For certain of our product candidates, 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 certain of 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.

With respect to our proprietary formulation of brexanolone, we have 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 brexanolone 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 brexanolone. 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 proprietary formulation of brexanolone is formulated in Captisol. Termination of our license agreement with CyDex would have a material adverse impact on our ability to develop and commercialize brexanolone in its current formulations.

In June 2015, we entered into an exclusive license agreement with The Regents of the University of California, or 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 are also party to a non-exclusive license with 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 status epilepticus, or 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 status epilepticus, essential tremor and/or postpartum depression. This agreement requires us to pay milestone payments in connection with the first derived product, which would include ZULRESSO, 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 ZULRESSO.

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, 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 materially 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 agreement with 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 new chemical entity or other types of marketing and data exclusivity for ZULRESSO or our other product candidates and if we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent terms of our product candidates, our business may be materially harmed.

Marketing exclusivity provisions under the Federal Food, Drug, and Cosmetic Act, or FDCA, can 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 U.S. 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. We plan to seek NCE exclusivity for brexanolone, and our other product candidates. There is also no guarantee that brexanolone or any of our other product candidates will qualify for marketing or data exclusivity under these provisions or that such exclusivity will alone be sufficient to for our business. 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.

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. Even if, at the relevant time, we have a valid issued patent covering our product, we may not be granted an extension if we were, for example, to fail to apply within applicable deadlines, to fail to apply prior to expiration of relevant patents or otherwise to fail to satisfy applicable requirements. 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.

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.

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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 we plan for a potential commercial launch of our product candidates, 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 to 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 or in obtaining regulatory approval 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, sale or commercial use. 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 $10.0 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. 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.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

The Tax Cuts and Jobs Act, or the TCJA, significantly reformed the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation, including a reduction of the corporate tax rate from a top marginal tax rate of 35% to a flat rate of 21%, a migration from a “worldwide” system of taxation to a territorial system, a limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), a limitation of the deduction for net operating losses to 80% of annual taxable income and an elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely) and the modification or repeal of many business deductions and credits (including a reduction the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as “orphan drugs”). As a result of the enacted law, the Company was required to revalue deferred tax assets and liabilities existing as of December 31, 2017 from the 34% federal rate in effect through the end of 2017, to the new 21% rate. This revaluation resulted in a reduction to the Company’s deferred tax asset of $66.4 million as of December 31, 2017. This amount was offset by a corresponding reduction to the Company’s valuation allowance. The other provisions of the TCJA did not have a material impact on the December 31, 2017 consolidated financial statements. Our final determination of the immediate TCJA impact and the remeasurement of our deferred assets and liabilities was completed prior to the deadline of one year from the enactment of the TCJA. For the year ended December 31, 2018, there were no material changes to our analysis originally performed as of December 31, 2017. We continue to examine the future impact of this tax reform legislation on our business. The impact of any tax reform, including any further tax reform that could be enacted in the future, is uncertain and could be adverse.

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

As of December 31, 2018, we had federal and state net operating loss carryforwards of $755.0 million and $760.7 million, respectively, which begin to expire in 2031 and 2030, respectively. As of December 31, 2018, we also had federal and state research and development tax credit carryforwards of $20.3 million and $4.1 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2018, we had federal orphan drug tax credit carryforwards of $40.0 million, which begin to expire in 2034. Under Section 382 of the Code, and similar state tax law, 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, whether as the result of our initial public offering, follow-on offerings, prior private placements, sales of our common stock by certain of our existing stockholders or additional sales of our common stock by us, may significantly reduce our ability to utilize our net operating loss carryforwards and research and development tax credit carryforwards before they expire and could have a material adverse effect on our results of operations in future years. We have performed an analysis of ownership changes through December 31, 2016 and believe that there have been changes in ownership in accordance with Section 382. However, we do not expect that

these changes in ownership will materially impact our ability to utilize our net operating loss carryforwards, research and development credits or orphan drug credits, prior to their expiration, although there can be no assurance in this regard. Subsequent ownership changes, as defined by Section 382, may potentially limit the amount of net operating loss carryforwards that could be utilized to offset future taxable income. Under the TCJA, net operating carryforwards generated after December 31, 2017 will not be subject to expiration.

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 could adversely impact 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 material 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 or cause us to have liability for disclosure of personal information of our customers. 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, if possible. 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 or prevented.

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. From our inception through December 31, 2018, we had received net proceeds of $1.6 billion from such transactions. As of December 31, 2018, our cash, cash equivalents and marketable securities were $922.8 million. We have incurred significant net losses in each year since our inception, including net losses of $372.9 million for the year ended December 31, 2018 and $270.1 million for the year ended December 31, 2017. 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 product revenue. To date, we have not generated any product 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 product 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;
- file for and receive marketing approval to commercialize our product candidates, if successfully developed;
- 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.

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 of ZULRESSO, if approved, and potentially other product candidates if successfully developed and approved. Developing small molecule products and preparing for a potential launch are expensive. We expect our research and development and general and administrative expenses to increase substantially in connection with our ongoing activities, particularly when and if we launch ZULRESSO and as we continue to advance our other product candidates in clinical trials, continue our discovery efforts, seek regulatory approval of our product candidates, if we generate positive data in our other clinical programs, and commercialize other products, if successfully developed and approved. Depending on the status of development efforts, 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, 2018, our cash, cash equivalents and marketable securities were $922.8 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 half of 2020. 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 equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to expand future development efforts, 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. In the event we receive negative data from our key clinical programs or encounter other major setbacks in our development or regulatory activities or in our commercialization efforts, if any of our product candidates are approved, our stock price is likely to decline which would make a future financing more difficult. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders. 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:

- the failure or delay of the FDA or any other regulatory authority to approve ZULRESSO or any of our other product candidates that are successfully developed, or any unexpected limitations on the approved indication or on use or onerous conditions of approval;
- plans for, progress of, timing of, changes to, delays in or results from, clinical trials or non-clinical studies of our SAGE-217 or any of our other product candidates, including positive or negative key data from such studies or clinical trials, serious adverse events arising in the course of development, or any delays or major announcements related to such studies or trials;
- 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.

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.

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Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate headquarters are located in Cambridge, Massachusetts. In October 2018, we entered into the Seventh Amendment to the Lease (the "Seventh Amendment") to increase the amount of square feet of office space that we lease in the multi-tenant building in which our headquarters are located. Prior to entering the Seventh Amendment, we rented 54,943 square feet of office space in this multi-tenant building under an operating lease that was scheduled to expire on August 15, 2024. The Seventh Amendment increased the amount of leased space at this location by 3,499 square feet beginning on December 1, 2018. The lease for this additional space will expire on August 31, 2024. Additionally, the term of the existing lease has been extended from August 15, 2024 until the expiration date of the Seventh Amendment on August 31, 2024.

In May 2016, we entered into a separate lease with an original expiration date of February 28, 2022, under which, beginning on September 1, 2016, we rent 19,805 square feet of additional office space in a separate multi-tenant building. In April 2018, we entered into the First Amendment to the lease for office space in this building. We increased the amount of square feet of office space from 19,805 square feet to 40,419 square feet, an increase of 20,614 square feet, consisting of (i) 13,481 square feet beginning on August 1, 2018, and (ii) 7,133 square feet beginning on October 1, 2018. The term for this additional space will expire on August 31, 2024. Additionally, the term of the existing lease was extended from February 28, 2022 until August 31, 2024. We have entered other non-material leases and 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 material 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.

Stockholders

As of February 12, 2019, there were four 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, 2018, 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 that 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 selected consolidated 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,				
	2018	2017	2016	2015	2014
	(in thousands, except share and per share data)				
Consolidated statements of operations data:					
Collaboration revenue	$90,273	$—	$—	$—	$—
Operating expenses:					
Research and development	282,107	210,277	120,756	69,357	24,100
General and administrative	201,404	62,878	39,407	25,293	9,710
Total operating expenses	483,511	273,155	160,163	94,650	33,810
Loss from operations	(393,238)	(273,155)	(160,163)	(94,650)	(33,810)
Interest income, net	20,334	3,099	1,211	178	8
Other income (expense), net	22	(64)	(35)	(23)	(9)
Net loss	(372,882)	(270,120)	(158,987)	(94,495)	(33,811)
Accretion of redeemable convertible preferred stock to redemption value	—	—	—	—	(2,294)
Net loss attributable to common stockholders	$(372,882)	$(270,120)	$(158,987)	$(94,495)	$(36,105)
Net loss per share attributable to common stockholders—basic and diluted(1)	$(8.08)	$(7.09)	$(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(1)	46,121,194	38,113,678	33,492,795	27,778,288	21,574,347

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	Year Ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands)				
Consolidated balance sheet data:					
Cash and cash equivalents	$190,943	$306,235	$168,517	$186,753	$127,766
Marketable securities	731,833	212,613	228,962	—	—
Working capital(2)	858,665	473,124	367,410	173,184	121,065
Total assets	952,705	529,937	404,531	189,016	129,665
Common stock and additional paid-in capital	1,827,026	1,066,064	688,963	335,035	188,730
Total stockholders' equity	862,971	475,475	368,517	173,695	121,885

(1) See Note 10 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.
(2) We define working capital as current assets less current liabilities.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of certain factors. We discuss factors that we believe could cause or contribute to these differences below and elsewhere in this report, including those set forth under Item 1A. "Risk Factors" and under "Cautionary Note Regarding Forward-Looking Statements" in this Annual Report on Form 10-K. We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the Securities and Exchange Commission, or SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

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 filing date of this Annual Report.

Our lead product candidate is ZULRESSO™ (brexanolone) injection, a proprietary intravenous, or IV, formulation of brexanolone for which we have filed a new drug application, or NDA, with the United States Food and Drug Administration, or the FDA, seeking approval to market and sell the product in the treatment of postpartum depression, or PPD. ZULRESSO is a proprietary formulation of allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors. PPD is a common biological complication of childbirth, and is characterized by significant depressive symptoms that typically commence during the third trimester of pregnancy or in the months following childbirth. Our NDA for ZULRESSO is currently under FDA review. On November 2, 2018, the Psychopharmacologic Drugs Advisory Committee, or PDAC, and Drug Safety and Risk Management, or DSaRM, Advisory Committee of the FDA jointly voted, by a vote of 17 to 1, that our data support a positive benefit/risk profile for ZULRESSO in the treatment of PPD when administered by qualified staff in a healthcare facility certified under a Risk Evaluation and Mitigation Strategies, or REMS, program. In November 2018, the FDA extended the previously disclosed December 19, 2018 Prescription Drug User Fee Act, or PDUFA, target date for a decision on the NDA for ZULRESSO by a period of three months to March 19, 2019. The launch of ZULRESSO in the U.S., if approved, will follow anticipated scheduling of brexanolone as a controlled substance by the Drug Enforcement Administration, or DEA, which we expect to be completed 90 days after FDA approval. We anticipate that ZULRESSO, if approved, will launch in the U.S. in June 2019. We currently have a sales, marketing, and market access teams in place in anticipation of a potential launch as well as a patient support team located in Raleigh, North Carolina. If approved, administration of ZULRESSO will be limited to healthcare facilities that have been certified under a REMS program under the supervision of qualified staff to mitigate the potential for harm associated with the risk of excessive sedation and loss of consciousness during administration of ZULRESSO. As part of the proposed REMS, patients who are prescribed ZULRESSO will be required to enroll in a patient registry to allow us to compile additional information to further our understanding of the risk of a loss of consciousness during administration and management of the risk. Given the mode of administration, the nature of the REMS and the limitation on the administration of ZULRESSO to a healthcare facility setting certified under the REMS, we expect that use of ZULRESSO, if approved for marketing and sale in the U.S., will, at least initially, be focused primarily on women with more severe symptoms of PPD, which we estimate is about 20 to 30% of women diagnosed with PPD.

We have received PRIority MEdicines, or PRIME, designation from the European Medicines Agency, or EMA, in the European Union, or EU, for our proprietary formulation of brexanolone as a potential treatment for PPD. In October 2018, we received scientific advice from the EMA regarding the potential regulatory pathway for a marketing authorization application, or MAA, filing in the EU. We anticipate having additional discussions with the EMA to help further clarify and evaluate what additional data and information would be needed, and what other requirements would need to be met, for a potential MAA filing.

Our next most advanced product candidate is SAGE-217, an oral compound that is currently in Phase 3 clinical development for PPD and major depressive disorder, or MDD. SAGE-217 is a novel neuroactive steroid that, like brexanolone, is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extrasynaptic $GABA_A$ receptors. The FDA has granted Breakthrough Therapy designation and Fast Track designation to SAGE-217 in the treatment of MDD. We have completed two positive placebo-controlled pivotal clinical trials with SAGE-217, one in MDD completed in 2017 and one in PPD for which top-line results were announced in January 2019. Our development plan for SAGE-217 is subject to ongoing discussions with the FDA. The ongoing Phase 3 clinical trials for SAGE-217 in MDD are: a placebo-controlled Phase 3 clinical trial in patients with MDD, known as the Mountain Study, in which we are studying two weeks of treatment with SAGE-217 followed by four weeks of follow-up and an ongoing open-label retreatment study, known as the Shoreline Study, evaluating initial treatment with SAGE-217, treatment-free intervals, and as needed retreatment, in patients with MDD in which patients will be followed for up to a year after treatment. Dosing in the Mountain Study commenced in December 2018, and we expect to report top-line results from this study in the fourth quarter of 2019 or the first quarter of 2020. We plan to add an open-label extension trial to the Mountain Study under a separate protocol to continue to follow patients from the Mountain Study after completion for up to six months. As part of our Phase 3 clinical development program for SAGE-217 in depression, we also plan to initiate a placebo-controlled trial to evaluate fixed interval SAGE-217 monotherapy (treatment without traditional antidepressants) for up to a year, which we believe will help us meet the expected

requirements for a potential NDA filing, and to include maintenance dosing as part of the label, if our development efforts are successful. In addition, we are conducting a placebo-controlled polysomnography Phase 3 clinical trial of SAGE-217 in patients with MDD who have co-morbid insomnia, known as the Rainforest Study. We expect to report top-line results from the Rainforest Study and the Shoreline Study in 2020.

We are also exploring SAGE-217 in other indications, including bipolar depression and sleep disorders. We expect to report topline results from a small open-label Phase 2 clinical trial of SAGE-217 in bipolar depression in the first half of 2019.

In addition to SAGE-217, we have a portfolio of other novel compounds that target $GABA_A$ receptors. SAGE-324 is a novel $GABA_A$ receptor positive allosteric modulator with preclinical pharmacokinetic and pharmacodynamic properties that suggest suitability for chronic oral dosing. We are considering developing SAGE-324 for a number of neurological conditions, including essential tremor and certain epileptiform disorders. Results from a recently completed Phase 1 single ascending dose clinical trial of SAGE-324 demonstrated that the profile of SAGE-324 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. SAGE-324 demonstrated clear target engagement in the brain using pharmaco-EEG (b-band power) as a functional biomarker. SAGE-324 was generally well-tolerated with no serious adverse events and with a safety profile consistent with $GABA_A$ positive allosteric modulation. A Phase 1 multiple ascending dose clinical trial of SAGE-324 is ongoing. We also recently initiated a Phase 1 clinical trial to determine the safety, tolerability and pharmacokinetics of SAGE-324 in a small number of patients with essential tremor. We expect to report top-line results from the Phase 1 multiple ascending dose clinical trial and the Phase 1 essential tremor clinical trial of SAGE-324 in the second half of 2019. Our portfolio also includes SAGE-689, a novel $GABA_A$ receptor positive allosteric modulator, with which we have conducted non-clinical studies to date, and other compounds 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, which we are exploring in certain cognition-related disorders impacted by NMDA receptor dysfunction, currently in Phase 1 development. Our initial areas of exploration for potential development of SAGE-718 will be indications involving NMDA receptor hypofunction. Indications involving NMDA receptor hypofunction include certain types, aspects or subpopulations of a number of diseases such as depression, Huntington's disease, Alzheimer's disease, attention deficit hyperactivity disorder, schizophrenia, and neuropathic pain. We completed a Phase 1 single ascending dose trial of SAGE-718 in 2017 and a Phase 1 multiple ascending dose trial in 2018. Results from these Phase 1 clinical trials of SAGE-718 demonstrated that the profile of SAGE-718 includes good oral bioavailability and a pharmacokinetic profile consistent with once-daily dosing. SAGE-718 was generally well-tolerated with no serious adverse events reported. We are continuing our SAGE-718 Phase 1 clinical program with target engagement biomarker studies in healthy volunteers, focused on electrophysiology and imaging, which are ongoing and for which we expect to report results in the first half of 2019. We also recently initiated a Phase 1 clinical trial to determine the safety, tolerability and pharmacokinetics of SAGE-718 in a small number of patients with early manifest Huntington's disease. We expect to report top-line results from this trial in the second half of 2019.

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, and movement, among others. We believe that we may 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 our 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 may 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 from the sale of products. All of our revenue to date has been derived from a strategic collaboration we entered into in the second quarter of 2018 with Shionogi & Co., Ltd., or Shionogi, for the clinical development and commercialization of SAGE-217 in Japan, Taiwan and South Korea. If approved in the U.S.,

we expect to establish a price for ZULRESSO within the range of $20,000 to $35,000 for the effective average list price per course of therapy. Given the anticipated U.S. launch of ZULRESSO in June 2019, and the time required to create pathways to care for ZULRESSO, we expect to start to see revenue momentum from sales of ZULRESSO, if approved, in the fourth quarter of 2019. We have incurred net losses in each year since our inception, and we have an accumulated deficit of $963.3 million as of December 31, 2018. Our net losses were $372.9 million, $270.1 million and $159.0 million

for the years ended December 31, 2018, 2017 and 2016, 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 and our commercial build. 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:

- continue preparations for a potential commercial launch of ZULRESSO in the treatment of PPD in the U.S., and commercialize the product, if approved;
- implement the REMS program and any post-approval requirements related to ZULRESSO, if our NDA is approved;
- continue to advance clinical development of SAGE-217, including the ongoing Phase 3 clinical program in MDD;
- continue to advance SAGE-324 through completion of Phase 1 clinical trials with potential future development in essential tremor, certain epileptiform disorders, and other neurological conditions;
- continue to advance SAGE-718, our early-stage novel allosteric modulator for NMDA, through completion of Phase 1 clinical trials, with potential future development in indications involving NMDA receptor hypofunction;
- advance one or more of our early clinical-stage product candidates into Phase 2 clinical development; and advance one or more of our non-clinical stage compounds into Phase 1 clinical development;
- continue our research and development efforts to evaluate the potential for our existing product candidates in the treatment of additional indications or in new formulations, and to identify new drug candidates in the treatment of CNS disorders;
- continue regulatory and other activities focused on further clarifying and evaluating the potential pathway for filing an MAA in the EU for our proprietary formulation of brexanolone as a treatment for PPD, including planned additional discussions with the EMA, and on identifying the regulatory pathway for development of SAGE-217 in the EU;
- seek regulatory approvals for any product candidates that successfully complete clinical development;
- continue to manufacture supplies of SAGE-217 for ongoing late stage clinical trials; improve the manufacturing process for our other product candidates; and manufacture clinical supplies as development progresses;
- add personnel, including personnel to support our product development and future commercialization efforts and potential future expansion of EU activities, and incur increases in stock-based compensation expense related to existing and new personnel with respect to both service-based and performance-based awards;
- evaluate market opportunities for our product candidates, including ZULRESSO in PPD, in other global markets;
- add operational, financial and management information systems; and
- maintain, leverage and expand our intellectual property portfolio.

As a result, we will need additional financing in the future 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 equity or debt financings or other sources, which may include collaborations with third parties. 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. Arrangements with collaborators or others may require us to relinquish

rights to certain of our technologies or product candidates. 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, 2018, will enable us to fund our operating expenses and capital expenditure requirements, based on our current operating plan, into the second half of 2020. See "—Liquidity and Capital Resources".

Financial Operations Overview

Revenue

We have not generated any revenue from product sales since our inception. 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. All of our revenue to date has been derived from our collaboration with Shionogi & Co., Ltd., or Shionogi. If we enter into additional collaboration agreements with third parties for our product candidates, we may generate revenue from those product candidates. We expect that revenue, if any, we generate under collaboration agreements will fluctuate from quarter to quarter due to the timing and amount of license fees, research and development services and related reimbursements, payments for clinical materials or manufacturing services, and milestone and other payments.

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. 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 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 for regulatory approval, 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, including salaries, benefits, stock-based compensation and travel expenses for 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 public relations, audit, tax and legal services, including legal expenses to pursue patent protection of our intellectual property.

We anticipate that our general and administrative expenses, including payroll and related expenses, will increase in the future as we continue to increase our headcount to support the expected growth in our business, expand our operations and organizational capabilities and prepare for the anticipated commercialization of ZULRESSO, if approved, and the potential commercialization of our other product candidates, if successfully developed. 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.

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.

Revenue

Effective January 1, 2017, we adopted Accounting Standards Codification, or ASC, Topic 606, Revenue from Contracts with Customers, or Topic 606. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases. Prior to the three months ended June 30, 2018, when we recorded our initial revenue under Topic 606, we did not have any revenue-generating arrangements and therefore there was no transition impact from the adoption of Topic 606.

Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services it transfers to a customer.

Once a contract is determined to be within the scope of Topic 606, we assess the goods or services promised within each contract and determine those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer's discretion are generally considered options. We assess if these options provide a material right to the customer and if so, they are considered performance obligations. The exercise of a material right may be accounted for as a contract modification or as a continuation of the contract for accounting purposes.

We assess whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct, in the evaluation of a collaboration agreement subject to Topic 606, we consider factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. We also consider the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, we are required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices, or SSP, on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, we consider applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. In certain circumstances, we may apply the residual method to determine the SSP of a good or service if the SSP is considered highly variable or uncertain. We validate the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, we estimate the amount of consideration to which we will be entitled in exchange for transferring the promised goods or services to a customer. We determine the amount of variable consideration by using the expected value method or the most likely amount method. We include the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction

price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, we re-evaluate the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, we evaluate whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

In determining the transaction price, we adjust consideration for the effects of the time value of money if the timing of payments provides us with a significant benefit of financing. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. We assessed our revenue-generating arrangement in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in the arrangement. For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, we recognize royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time this is based on the use of an output or input method.

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 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, including grants of stock options and restricted stock, made to employees and non-employee directors 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, using management's best estimates, which consider the inherent risk and uncertainty regarding the future outcomes of the milestones, 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. For grants of restricted stock units, we base the fair value on the stock price as of the date of grant.

We recognize compensation expense for stock-based awards granted to non-employee consultants based on the fair value of the award on each date on which the awards vest. Compensation expense is recognized over the vesting period, provided that services are rendered by such non-employee consultants during that time. At the end of each financial reporting period, the fair value of unvested options is re-measured using the then-current fair value of our common stock and updated assumptions in the Black-Scholes option-pricing model; and the fair value of restricted stock awards is re-measured using 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 amount of time that we had been 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 common stock. 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 non-employee consultants 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 that are 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 that 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,		
	2018	2017	2016
Expected dividend yield	0 %	0 %	0 %
Expected volatility	74.45 %	79.89 %	80.15 %
Risk-free interest rate	2.68 %	2.03 %	1.47 %
Expected life of option	6.04 years	6.03 years	6.05 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 recognized in the current period.

Stock-based compensation expense recognized during the years ended December 31, 2018, 2017 and 2016 was as follows:

	2018	2017	2016
	(in thousands)		
Research and development	$50,871	$19,893	$11,197
General and administrative	51,092	15,641	11,823
	$101,963	$35,534	$23,020

At December 31, 2018, we had unrecognized stock-based compensation expense related to our unvested service-based stock option awards of $282.6 million, which is expected to be recognized over the remaining weighted average vesting period of 2.88 years.

At December 31, 2018, 772,347 performance-based stock options were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to those awards was $50.1 million.

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, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017:

	Year Ended December 31,		Increase (Decrease)
	2018	2017	
	(in thousands)		
Collaboration revenue	$90,273	$—	$90,273
Operating expenses:			
Research and development	282,107	210,277	71,830
General and administrative	201,404	62,878	138,526
Total operating expenses	483,511	273,155	210,356
Loss from operations	(393,238)	(273,155)	(120,083)
Interest income, net	20,334	3,099	17,235

Other income (expense), net	22	(64)	86
Net loss	$(372,882)	$(270,120)	$(102,762)

Collaboration revenue

We have not generated any revenue from product sales since our inception. 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. All of our revenue to date has been derived from our collaboration with Shionogi & Co., Ltd., or Shionogi. If we enter into additional collaboration agreements with third parties for our product candidates, we may generate revenue from those product candidates. We expect that revenue, if any, we generate under collaboration agreements will fluctuate from quarter to quarter as a result of the timing and amount of license fees, research and development services and related reimbursements, payments for clinical materials or manufacturing services, and milestone and other payments.

Research and development expenses

	Year Ended December 31,		
	2018	2017	Increase (Decrease)
	(in thousands)		
brexanolone (SAGE-547)	$32,184	$79,950	$ (47,766)
SAGE-217	56,925	44,327	12,598
SAGE-718	13,576	5,691	7,885
Other research and development programs	46,045	13,625	32,420
Unallocated expenses	133,377	66,684	66,693
Total research and development expenses	$282,107	$210,277	$ 71,830

Research and development expenses for the year ended December 31, 2018 were $282.1 million, compared to $210.3 million for the year ended December 31, 2017. The increase of $71.8 million was primarily due to the following:

- a decrease of $47.8 million in expenses related to our brexanolone program, due to the completion of the Phase 3 clinical trial in super-refractory status epilepticus, or SRSE, and the Phase 3 clinical trials in PPD. Expenses related to payments to licensors upon achievement of certain clinical development milestones were $1.0 million in the year ended December 31, 2018. No expenses related to payments to licensors upon achievement of certain regulatory and clinical development milestones were incurred in the year ended December 31, 2017;

- an increase of $12.6 million in expenses related to conduct of our Phase 3 clinical trial of SAGE-217 in PPD and conduct of clinical pharmacology studies to support the clinical trials for SAGE-217;

- an increase of $7.9 million in expenses related to conduct of our Phase 1 clinical trials of SAGE-718 and supporting clinical activities;

- an increase of $32.4 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 $66.7 million in unallocated expenses, mainly due to the hiring of additional full-time employees to support the growth of our operations, including an increase of $31.0 million of non-cash stock-based compensation and an increase of $28.3 million in other employee-related costs, mainly for salaries. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $2.5 million for the year ended December 31, 2018. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the year ended December 31, 2017.

General and administrative expenses

	Year Ended December 31,		Increase (Decrease)
	2018	2017	
	(in thousands)		
Personnel-related	$113,702	$33,240	$80,462
Professional fees	24,702	12,162	12,540
Commercial planning	44,598	11,176	33,422
Other	18,402	6,300	12,102
Total general and administrative expenses	$201,404	$62,878	$138,526

General and administrative expenses for the years ended December 31, 2018 and 2017 were $201.4 million and $62.9 million, respectively. The increase of $138.5 million was primarily due to the following:

- an increase of $80.5 million in personnel-related costs in connection with the hiring of additional full-time employees to support the growth of our operations, including an increase of $35.5 million of non-cash stock-based compensation and an increase of $49.4 million in other employee-related costs, mainly for salaries. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $8.9 million during the year ended December 31, 2018. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the year ended December 31, 2017;

- an increase of $12.5 million in professional fees associated with expanding operations, including costs related to legal services, including legal expenses to pursue patent protection of our intellectual property; public relations and accounting services;

- an increase of $33.4 million in costs related to preparations for an anticipated commercial launch, if we are successful in our efforts to obtain regulatory approval of ZULRESSO in the U.S.; and

- an increase of $12.1 million in other expenses 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 increased number of employees, along with other corporate infrastructure and office-related costs.

Interest income, net and other expense, net

Interest income, net, and other expense, net, for the years ended December 31, 2018 and 2017 were $20.4 million and $3.0 million, respectively. The primary reasons for the increase were increases in the balances of marketable securities and interest rates.

Comparison of the Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016:

	Year Ended December 31,		Increase (Decrease)
	2017	2016	
	(in thousands)		
Collaboration revenue	$—	$—	$—
Operating expenses:			
Research and development	210,277	120,756	89,521

General and administrative	62,878	39,407	23,471
Total operating expenses	273,155	160,163	112,992
Loss from operations	(273,155)	(160,163)	(112,992)
Interest income, net	3,099	1,211	1,888
Other expense, net	(64)	(35)	(29)
Net loss	$(270,120)	$(158,987)	$(111,133)

Research and development expenses

	Year Ended December 31,		Increase (Decrease)
	2017	2016	
		(in thousands)	
brexanolone (SAGE-547)	$79,950	$ 54,363	$ 25,587
SAGE-217	44,327	18,668	25,659
SAGE-718	5,691	6,457	(766)
Other research and development programs	13,625	9,594	4,031
Unallocated expenses	66,684	31,674	35,010
Total research and development expenses	$210,277	$ 120,756	$ 89,521

Research and development expenses for the year ended December 31, 2017 were $210.3 million, compared to $120.8 million for the year ended December 31, 2016. The increase of $89.5 million was primarily due to the following:

- an increase of $25.6 million in expenses related to our brexanolone program, due to the continued advancement of the program in clinical development, including conduct of the Phase 3 clinical trials in SRSE and the Phase 3 clinical trials in PPD; conduct of supporting clinical pharmacology studies; an increase in chemistry, manufacturing and control, or CMC, work in preparation for a potential filing for regulatory approval; and an estimate of future remaining costs for the close-out of the Phase 3 clinical trial in SRSE. No expenses related to payments to consultants and licensors upon achievement of certain clinical development milestones were incurred in the year ended December 31, 2017. Expenses related to payments to consultants and licensors upon achievement of certain clinical development milestones were $0.8 million for the year ended December 31, 2016;
- an increase of $25.7 million in expenses related to conduct of our Phase 2 clinical trials of SAGE-217 in MDD, essential tremor, Parkinson's disease and PPD, conduct of supporting clinical pharmacology studies and production of clinical supply to support these clinical trials;
- a decrease of $0.8 million in expenses related to conduct of our Phase 1 clinical trial of SAGE-718 due to the timing of certain activities;
- an increase of $4.0 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 $35.0 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 $8.7 million of non-cash stock-based compensation and an increase of $20.4 million in other employee-related costs, mainly for salaries. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the year ended December 31, 2017. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $2.3 million for the year ended December 31, 2016.

General and administrative expenses

	Year Ended		Increase

	December 31,		
	2017	2016	(Decrease)
		(in thousands)	
Personnel-related	$33,240	$ 22,107	$ 11,133
Professional fees	12,162	6,941	5,221
Commercial planning	11,176	5,268	5,908
Other	6,300	5,091	1,209
Total general and administrative expenses	$62,878	$ 39,407	$ 23,471

General and administrative expenses for the years ended December 31, 2017 and 2016 were $62.9 million and $39.4 million, respectively. The increase of $23.5 million was primarily due to the following:

- an increase of $11.1 million in personnel-related costs in connection with the hiring of additional full-time employees to support operations, finance, human resources, legal and planned commercial activities. There was no non-cash stock-based compensation expense recognized related to the achievement of performance-based vesting criteria during the year ended December 31, 2017. The amount of non-cash stock-based compensation expense related to the achievement of performance-based vesting criteria was $2.7 million for the year ended December 31, 2016;
- an increase of $5.2 million in professional fees associated with expanding operations, including costs related to audit, legal, and tax-related services, as well as investor relations costs;
- an increase of $5.9 million in costs related to preparations for an anticipated commercial launch, if we are successful in our efforts to file an NDA and obtain regulatory approval of ZULRESSO in the U.S.; and
- an increase of $1.2 million in other expenses 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 increased number of employees.

Interest income, net and other expense, net

Interest income, net, and other expense, net, for the years ended December 31, 2017 and 2016 were $3.0 million and $1.2 million, respectively. The primary reason for the increase was the increase in interest income because we owned marketable securities throughout the year ended December 31, 2017, after making our initial purchase of marketable securities during the year ended December 31, 2016.

Liquidity and Capital Resources

Since our inception in April 2010, we have not generated any revenue from the sale of products. All of our revenue to date has been derived from our collaboration with Shionogi. To date, we have incurred recurring net losses. As of December 31, 2018, we had an accumulated deficit of $963.3 million. From our inception through December 31, 2018, we received net proceeds of $1.6 billion from the sales of redeemable convertible preferred stock, the issuance of convertible notes and the sales of common stock in our IPO in July 2014 and follow-on offerings in April 2015, January 2016, September 2016, November 2017 and February 2018.

On November 17, 2017, we completed the sale of 4,058,822 shares of our common stock in an underwritten public offering at a price to the public of $85.00 per share, resulting in net proceeds of $325.8 million after deducting commissions and underwriting discounts and offering costs paid by us.

On February 13, 2018, we completed the sale of 4,032,012 shares of our common stock in an underwritten public offering at a price to the public of $164.00 per share, resulting in net proceeds of $631.2 million after deducting commissions and underwriting discounts and offering costs paid by us.

As of December 31, 2018, our primary sources of liquidity were our cash, cash equivalents and marketable securities, which totaled $922.8 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.

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The following table summarizes the primary sources and uses of cash for the years ended December 31, 2018, 2017 and 2016:

	Year ended December 31,		
	2018	2017	2016
	(in thousands)		
Net cash provided by (used in):			
Operating activities	$(260,671)	$(219,277)	$(118,678)
Investing activities	(512,461)	15,462	(230,015)
Financing activities	659,358	341,818	330,982
Total	$(113,774)	$138,003	$(17,711)

Operating activities

Cash used in operating activities for the year ended December 31, 2018 was $260.7 million, compared to $219.3 million for the year ended December 31, 2017. The increase of $41.4 million was primarily due to the following:

- An increase of $102.8 million in cash used related to our net loss, primarily due to $90.3 million of collaboration revenue that was recorded during the year ended December 31, 2018, offset by an increase in research and development activities related to our development programs along with increased headcount in related functions, and increased general and administrative expenses due to increased headcount and other costs to support our expanding operations;
- Offset by an increase of $57.3 million in non-cash charges, primarily due to an increase in stock-based compensation expense due to increased hiring and an increase in the fair market value of our common stock; and
- Offset by an increase of $4.0 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 year ended December 31, 2017 was $219.3 million, compared to $118.7 million for the year ended December 31, 2016. The increase of $100.6 million was primarily due to the following:

- An increase of $111.1 million in cash used related to our net loss, primarily due to increased research and development activities related to our lead development programs along with increased headcount in related functions, and increased general and administrative expenses due to increased headcount and other costs to support our expanding operations;
- Offset by an increase of $12.8 million in non-cash charges, primarily due to an increase in stock-based compensation expense due to increased hiring during the year, and
- Offset by an increase of $2.3 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, 2018 and 2017, net cash used in investing activities was $512.5 million and net cash provided by investing activities was $15.5 million, respectively. During the year ended December 31, 2018, we purchased marketable securities and had sales and maturities of our marketable securities as part of managing our cash and investments portfolio, including purchases using proceeds received in our underwritten follow-on public offering during February 2018.

During the years ended December 31, 2017 and 2016, net cash provided by investing activities was $15.5 million and net cash used by investing activities was $230.0 million, respectively. During the year ended December 31, 2017, we purchased and sold marketable securities, as part of managing our cash and investments portfolio. 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.

Financing activities

During the years ended December 31, 2018, 2017 and 2016, net cash provided by financing activities was $659.4 million, $341.8 million and $331.0 million, respectively.

- Net cash provided by financing activities in the year ended December 31, 2018 primarily consisted of $631.2 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, 2017 primarily consisted of $325.8 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, 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.

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. Given the anticipated June 2019 launch of ZULRESSO and the time required to create pathways to care for ZULRESSO, we expect to start to see revenue momentum from sales of ZULRESSO, if approved, in the fourth quarter of 2019. 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; begin to commercialize any products, if successfully developed and approved; and continue our efforts to identify and develop new product candidates. We also 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, 2018, will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2020. During that time, we expect that our expenses will increase substantially as we:

- continue preparations for a potential future commercial launch of ZULRESSO in the U.S, and commercialize the product, if approved;
- implement the REMS program and any post-approval requirements related to ZULRESSO, if our NDA is approved;
- continue to advance clinical development of SAGE-217, including the ongoing Phase 3 clinical program in MDD;
- continue to advance SAGE-324 through completion of Phase 1 clinical trials with potential future development in essential tremor, certain epileptiform disorders, and other neurological conditions;
- continue to advance SAGE-718, our early-stage novel allosteric modulator for NMDA, through completion of Phase 1 clinical trials, with potential future development in indications involving NMDA receptor hypofunction;
- advance one or more of our early clinical-stage product candidates into Phase 2 clinical development; and advance one or more of our non-clinical stage compounds into Phase 1 clinical development;
- continue our research and development efforts to evaluate the potential for our 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;
- continue regulatory and other activities focused on further clarifying and evaluating the potential pathway for filing an MAA in the EU for our proprietary formulation of brexanolone as a treatment for PPD, including planned

additional discussions with the EMA, and on identifying the regulatory pathway for development of SAGE-217 in the EU;

- seek regulatory approvals for any product candidates that successfully complete clinical development;
- continue to improve the manufacturing process for our product candidates; and manufacture clinical supplies as development progresses;
- add personnel, including personnel to support our product development and future commercialization efforts, and potential expansion of EU activities, and incur increases in stock compensation expense related to existing and new personnel with respect to both service-based and performance-based awards;
- evaluate market opportunities for ZULRESSO in PPD in other global markets;
- 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 or other 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 outcome of the FDA's review of our NDA for ZULRESSO, and the scope and cost of any clinical trials or other commitments required post-approval;
- the level, timing and amount of costs associated with preparing for a potential future commercial launch of ZULRESSO in the near term, and, if we are successful in obtaining regulatory approval, the cost of executing a commercial launch of ZULRESSO;
    - the rate, degree and level of market acceptance for ZULRESSO in the treatment of PPD in the U.S., if approved, including the impact of factors such as: availability of sites of care to be certified under our REMS program for administration of ZULRESSO; the level of pricing and reimbursement; the number of healthcare professionals willing to prescribe ZULRESSO and the number of women with PPD who agree to be treated with ZULRESSO; and the amount and timing of revenues from sales of ZULRESSO in the U.S. if we are successful in our commercialization efforts;
- the ability of SAGE-217 and our other clinical-stage product candidates to progress through clinical development successfully; the timing, scope and outcome of regulatory filings, reviews and approvals of such product candidates, if we are successful in our development efforts; the scope and cost of any clinical trials or other commitments required post-approval for any approved products; and the level, timing and amount of costs associated with preparing for a potential future commercial launch of any such product candidate that is successfully developed and approved;
- 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 outcome of regulatory and other discussions and activities focused on potential pathways for advancing our product candidates in the EU and other markets outside the U.S., and the scope and timing of resulting decisions and plans, if any, we make to build or expand in those markets;
- at such time, if any, that we have approved products, the size of the indications for which those products are approved; the portion of the population for which those products are actually prescribed; the rate and degree of market acceptance for those products, and the pricing, availability and level of reimbursement for such products;
- the number and characteristics of the product candidates we pursue in development and the nature and scope of our discovery and development programs;

- 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 and achieve profitability, 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 or other means 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, 2018 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)	$47,681	$7,918	$16,762	$17,586	$5,415
Total[(1)(2)(3)]	$47,681	$7,918	$16,762	$17,586	$5,415

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. We do not include amounts related to milestones for indications that we are no longer pursuing.

(1) We lease office space in two multi-tenant buildings in Cambridge, Massachusetts, consisting, as of December 31, 2018, of 58,442 square feet in the first building under an operating lease that will expire on August 31, 2024 and 19,805 square feet in the second building under an operating lease that will expire on August 31, 2024. In April

2018, we entered into the First Amendment to the lease for office space in the second multi-tenant building and thereby increased the amount of square feet of office space from 19,805 square feet to 40,419 square feet, an increase of 20,614 square feet, consisting of (i) 13,481 square feet that began on August 1, 2018, and (ii) 7,133 square feet that began on October 1, 2018. The term for this additional space will expire on August 31, 2024. Additionally, the term of the existing lease was extended from February 28, 2022 until August 31, 2024. In May 2018, the Company entered into a lease for office space in a multi-tenant building in Raleigh, North Carolina. The amount of square feet of office space is 15,525 square feet and the lease period began on September 1, 2018. The term for this space will expire on November 30, 2024. In October 2018, we entered into the Seventh Amendment to the lease for office space in the first building and thereby increased the amount of square feet of office space from 54,943 square feet to 58,442 square feet. The increase of 3,499 square feet began on December 1, 2018. The term for this additional space will expire on August 31, 2024. In December 2018, we entered into a lease in a third multi-tenant building in Cambridge, Massachusetts, for 15,975 square feet of office space which will begin on March 1, 2019. The term for this lease will expire on February 28, 2024. We expect to lease additional space prior to the expiration of our leases to meet the needs of the business. The minimum lease payments in the table do not include related common area maintenance costs 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 $28.7 million upon achieving certain milestones, related to clinical development, regulatory approvals and sales. For the year ended December 31, 2018, we recorded $1.0 million of research and development expense under these license agreements.

(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.

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 $922.8 million as of December 31, 2018. 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 operations. We do not own any derivative financial instruments.

We contract with vendors in foreign countries and have subsidiaries in Europe. As such, we have exposure to adverse changes in exchange rates of foreign currencies associated with our foreign transactions. We believe this exposure to be immaterial. We do not hedge against this exposure to fluctuations in exchange rates.

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, 2018.

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, 2018, 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, 2018, 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 Securities Exchange Act of 1934). 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, 2018 and concluded that it was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2018 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.

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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 2019 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 2019 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 2019 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 2019 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 2019 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.

Report of Independent Registered Public Accounting Firm

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

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Sage Therapeutics, Inc. and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, of changes in stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2018, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2018, based on criteria established in Internal Control - Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018 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, 2018, based on criteria established in Internal Control - Integrated Framework (2013) issued by the COSO.

Basis for Opinions

The Company's management is responsible for these consolidated 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 the accompanying Management's Report on Internal Control over Financial Reporting. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. 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.

Definition and Limitations of Internal Control over Financial Reporting

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 19, 2019

We have served as the Company's auditor since 2013.

Sage Therapeutics, Inc. and Subsidiaries

Consolidated Balance Sheets

(in thousands, except share and per share data)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$190,943	$306,235
Marketable securities	731,833	212,613
Prepaid expenses and other current assets	21,919	6,227
Total current assets	944,695	525,075
Property and equipment, net	5,643	4,013
Restricted cash	2,367	849
Total assets	$952,705	$529,937
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$34,036	$9,350
Accrued expenses	51,994	42,601
Total current liabilities	86,030	51,951
Other liabilities	3,704	2,511
Total liabilities	89,734	54,462
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.0001 par value per share; 5,000,000 shares authorized at December 31, 2018 and 2017; no shares issued or outstanding at December 31, 2018 and 2017	—	—
Common stock, $0.0001 par value per share; 120,000,000 shares authorized at December 31, 2018 and 2017; 46,891,296 and 42,003,894 shares issued at December 31, 2018 and 2017, respectively; 46,888,263 and 42,002,934 shares outstanding at December 31, 2018 and 2017, respectively	5	5
Treasury stock, at cost, 3,033 and 960 shares at December 31, 2018 and December 31, 2017, respectively	(211)	(113)
Additional paid-in capital	1,827,021	1,066,059
Accumulated deficit	(963,329)	(590,447)
Accumulated other comprehensive loss	(515)	(29)
Total stockholders' equity	862,971	475,475
Total liabilities and stockholders' equity	$952,705	$529,937

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,		
	2018	2017	2016
Collaboration revenue	$90,273	$—	$—
Operating expenses:			
Research and development	282,107	210,277	120,756
General and administrative	201,404	62,878	39,407
Total operating expenses	483,511	273,155	160,163
Loss from operations	(393,238)	(273,155)	(160,163)
Interest income, net	20,334	3,099	1,211
Other income (expense), net	22	(64)	(35)
Net loss	$(372,882)	$(270,120)	$(158,987)
Net loss per share—basic and diluted	$(8.08)	$(7.09)	$(4.75)
Weighted average number of common shares outstanding—basic and diluted	46,121,194	38,113,678	33,492,795
Comprehensive loss:			
Net loss	$(372,882)	$(270,120)	$(158,987)
Other comprehensive items:			
Unrealized gain (loss) on marketable securities	(486)	73	(102)
Total other comprehensive gain (loss)	(486)	73	(102)
Total comprehensive loss	$(373,368)	$(270,047)	$(159,089)

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

Sage Therapeutics, Inc. and Subsidiaries

Consolidated Statements of Changes in Stockholders' Equity

(in thousands, except share data)

	Common Stock		Treasury Stock		Additional Paid-in	Accumulated Other Comprehensive	Accumulated	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Income (Loss)	Deficit	Equity
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 awards	42,781	—	—	—	11	—	—	11
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
Issuance of common stock from exercise of stock options	706,222	1	—	—	15,436	—	—	15,437
Issuance of common stock under employee stock purchase plan	15,718	—	—	—	771	—	—	771
Purchase of treasury stock	—	—	614	(96)	—	—	—	(96)
Stock-based compensation expense	—	—	—	—	35,142	—	—	35,142
	4,058,822	—	—	—	325,751	—	—	325,751

Public offering of common stock, net of offering costs								
Unrealized gain on available-for-sale securities	—	—	—	—	—	73	—	73
Net loss	—	—	—	—	—	—	(270,120)	(270,120)
Balances at December 31, 2017	42,002,934	5	960	(113)	1,066,059	(29)	(590,447)	475,475
Issuance of common stock from exercise of stock options	824,188	—	—	—	27,014	—	—	27,014
Issuance of common stock under employee stock purchase plan	19,687	—	—	—	2,705	—	—	2,705
Purchase of treasury stock	—	—	2,073	(98)	—	—	—	(98)
Stock-based compensation expense	—	—	—	—	100,993	—	—	100,993
Public offering of common stock, net of offering costs	4,032,012	—	—	—	631,154	—	—	631,154
Unrealized loss on available-for-sale securities	—	—	—	—	—	(486)	—	(486)
Vesting of restricted stock units, net of employee tax obligations	9,442	—	—	—	(904)	—	—	(904)
Net loss	—	—	—	—	—	—	(372,882)	(372,882)
Balances at December 31, 2018	46,888,263	$ 5	3,033	$ (211)	$ 1,827,021	$ (515)	$ (963,329)	$ 862,971

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,		
	2018	2017	2016
Cash flows from operating activities			
Net loss	$(372,882)	$(270,120)	$(158,987)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	101,963	35,534	23,020
Premium on marketable securities	(215)	(105)	(756)
Amortization of premium (discount) on marketable securities	(9,892)	(293)	286
Depreciation	1,143	531	281
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(15,462)	(1,127)	(3,362)
Accounts payable	24,544	(3,693)	7,796
Accrued expenses and other liabilities	10,130	19,996	13,044
Net cash used in operating activities	(260,671)	(219,277)	(118,678)
Cash flows from investing activities			
Proceeds from sales and maturities of marketable securities	974,757	261,225	30,499
Purchases of marketable securities	(1,484,358)	(244,403)	(259,093)
Purchases of property and equipment	(2,860)	(1,360)	(1,421)
Net cash provided by (used in) investing activities	(512,461)	15,462	(230,015)
Cash flows from financing activities			
Proceeds from stock option exercises and employee stock purchase plan issuances	29,108	15,972	1,406
Payment of employee tax obligations related to vesting of restricted stock units	(904)	—	
Payments of offering costs	(340)	(179)	(599)
Proceeds from public offerings of common stock, net of commissions and underwriting discounts	631,494	326,025	330,175
Net cash provided by financing activities	659,358	341,818	330,982
Net increase (decrease) in cash, cash equivalents and restricted cash	(113,774)	138,003	(17,711)
Cash, cash equivalents and restricted cash at beginning of period	307,084	169,081	186,792
Cash, cash equivalents and restricted cash at end of period	$193,310	$307,084	$169,081
Supplemental disclosure of non-cash operating, investing and financing activities			
Landlord tenant incentive included in other current assets	$229	$—	$—
Purchases of property and equipment financed with landlord tenant	$—	$1,665	$—

incentive			
Purchases of property and equipment included in accounts payable	$51	$138	$8
Public offering costs included in accounts payable	$—	$95	$—

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

SAGE THERAPEUTICS, INC. AND SUBSIDIARIES

Notes to 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 ("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.

The Company is subject to risks and uncertainties common to companies in the biotech and pharmaceutical 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 approved for marketing and sale; 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.

Under Accounting Standards Update ("ASU") 2014-15, Presentation of Financial Statements—Going Concern (Subtopic 205-40), or ASC 205-40, the Company has the responsibility to evaluate whether conditions and/or events raise substantial doubt about its ability to meet its future financial obligations as they become due within one year after the date that the financial statements are issued. The Company has incurred losses and negative cash flows from operations since its inception. As of December 31, 2018, the Company had an accumulated deficit of $963.3 million. From its inception through December 31, 2018, the Company received net proceeds of $1.6 billion from the sales of redeemable convertible preferred stock, the issuance of convertible notes, and the sales of common stock in its initial public offering ("IPO") in July 2014 and follow-on public offerings in April 2015, January 2016, September 2016, November 2017 and February 2018. Until such time, if ever, as the Company can generate substantial product revenue and achieve profitability, 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.

The Company expects that, based on its current operating plans, the Company's existing cash, cash equivalents and marketable securities will be sufficient to fund its current planned operations for at least the next twelve months from the issuance of these consolidated financial statements. At some point after that time, the Company will require additional financing to fund its future operations.

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 90 days or less at the date of purchase to be cash equivalents. As of December 31, 2018, cash equivalents were comprised of cash equivalents and money market funds. As of December 31, 2017, cash equivalents were comprised of cash equivalents, money market funds and overnight reverse repurchase agreements.

Marketable securities

Marketable securities consist of investments with original maturities greater than 90 days. The Company has classified its investments with maturities beyond one year as short-term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. 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 several 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 years ended December 31, 2018 and December 31, 2017.

Restricted Cash

For the initial facility of the Company, a deposit of $39,000 was restricted from withdrawal as of December 31, 2018 and 2017. The restriction is related to securing the initial lease and the restriction will expire in 2024, in accordance with the most recent amendment to the operating lease agreement. A deposit of $0.3 million was restricted from withdrawal as of December 31, 2018 and 2017. The restriction is related to securing an amendment to the lease of the initial facility of the Company and the restriction will expire in 2024, in accordance with the most recent amendment to the operating lease agreement. These balances are included in restricted cash on the accompanying consolidated balance sheets.

A deposit of $0.5 million was restricted from withdrawal as of December 31, 2018 and 2017. The restriction is related to securing the separate facility lease on the second multi-tenant building in May 2016 and the restriction will expire in 2024, in accordance with the most recent amendment to the operating lease agreement. A deposit of $0.4 million was restricted from withdrawal as of December 31, 2018. The restriction is related to securing an amendment to the lease of the separate facility of the Company and the restriction will expire in 2024, in accordance with the most

recent amendment to the operating lease agreement. These balances are included in restricted cash on the accompanying consolidated balance sheets.

A deposit of $0.4 million was restricted from withdrawal as of December 31, 2018. The restriction is related to securing a separate facility lease on the third multi-tenant building in December 2018 that will expire on February 28, 2024, under which, beginning on March 1, 2019, the Company will rent 15,975 square feet of additional office space. The restriction will expire in 2024, in accordance with the operating lease agreement. This balance is included in restricted cash on the accompanying consolidated balance sheet.

A deposit of $0.7 million was restricted from withdrawal as of December 31, 2018. The restriction is related to securing leases on automobiles for employees who are based in the field. The restriction will expire in 2021, in accordance with the 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.

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 costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research and development 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 estimates made by the Company. The historical accrual estimates made by the Company 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 consolidated statements of operations and comprehensive loss.

Stock-Based Compensation

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

The Company recognizes compensation expense for stock-based awards granted to non-employee consultants based on the fair value of the award on each date on which the awards vest. Compensation expense is recognized over the vesting period, provided that services are rendered by such non-employee consultants during that time. At the end of each financial reporting period, the fair value of unvested options is re-measured using the then-current fair value of the common stock of the Company and updated assumptions in the Black-Scholes option-pricing model; and the fair value of restricted stock awards is re-measured using the then-current fair value of the common stock of the Company.

For awards that vest upon achievement of a performance condition, the Company recognizes 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.

The fair value of each option grant is estimated using the Black-Scholes option-pricing model. Through December 31, 2015, the Company lacked sufficient Company-specific historical and implied volatility information, and as a result, the Company used the volatility of a group of publicly-traded peer companies in the Black-Scholes calculations. Beginning in 2016, the Company estimated 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 options granted by the Company 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 non-employee directors 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 has 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. Expected forfeitures are based on the historical experience of the Company and management's expectations of future forfeitures. To the extent actual forfeitures differ from the estimates, the difference is 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.

Treasury Stock

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

Basic and Diluted Net Loss Per Share

Basic net loss per share is computed by dividing the net loss by the weighted average number of common shares outstanding for the period. For periods in which the Company has reported net losses, diluted net loss per share is the same as basic net loss per share, because dilutive common shares are not assumed to have been issued if their effect is antidilutive.

The Company reported a net loss for the years ended December 31, 2018, 2017 and 2016.

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 current and future product

candidates of the Company 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, cash equivalents and marketable securities. The Company maintains accounts for all cash and cash equivalents at 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. 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.

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, 2018 and 2017 were carried at fair value, determined according to the fair value hierarchy; see Footnote 3, Fair Value Measurements herein.

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, 2018 and 2017, respectively.

Segment Data

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

Comprehensive Loss

Comprehensive loss includes net loss and other changes in stockholders' equity that result from transactions and economic events other than those with stockholders.

Public Offerings

On July 23, 2014, the Company completed the sale of 5,750,000 shares of its common stock in its 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 the Nasdaq Global Market on July 18, 2014.

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 paid by the Company.

On November 17, 2017, the Company completed the sale of 4,058,822 shares of its common stock at a price to the public of $85.00 per share, resulting in net proceeds to the Company of $325.8 million after deducting underwriting discounts and commissions and offering costs paid by the Company.

On February 13, 2018, the Company completed the sale of 4,032,012 shares of its common stock at a price to the public of $164.00 per share, resulting in net proceeds to the Company of $631.2 million after deducting underwriting discounts and commissions and offering costs paid by the Company.

Revenue Recognition

Effective January 1, 2017, the Company adopted Accounting Standards Codification (“ASC”), Topic 606, Revenue from Contracts with Customers (“Topic 606”). This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases. Prior to the three months ended June 30, 2018, when the Company recorded its initial revenue under Topic 606, the Company did not have any revenue-generating arrangements and therefore there was no transition impact from the adoption of Topic 606.

Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps: (i) identify the contract with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to contracts when it is probable that the Company will collect the consideration to which it is entitled in exchange for the goods or services it transfers to a customer.

Once a contract is determined to be within the scope of Topic 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations. Arrangements that include rights to additional goods or services that are exercisable at a customer’s discretion are generally considered options. The Company assesses if these options provide a material right to the customer and if so, they are considered

performance obligations. The exercise of a material right may be accounted for as a contract modification or as a continuation of the contract for accounting purposes.

The Company assesses whether each promised good or service is distinct for the purpose of identifying the performance obligations in the contract. This assessment involves subjective determinations and requires management to make judgments about the individual promised goods or services and whether such are separable from the other aspects of the contractual relationship. Promised goods and services are considered distinct provided that: (i) the customer can benefit from the good or service either on its own or together with other resources that are readily available to the customer (that is, the good or service is capable of being distinct) and (ii) the entity's promise to transfer the good or service to the customer is separately identifiable from other promises in the contract (that is, the promise to transfer the good or service is distinct within the context of the contract). In assessing whether a promised good or service is distinct in the evaluation of a collaboration arrangement subject to Topic 606, the Company considers factors such as the research, manufacturing and commercialization capabilities of the collaboration partner and the availability of the associated expertise in the general marketplace. The Company also considers the intended benefit of the contract in assessing whether a promised good or service is separately identifiable from other promises in the contract. If a promised good or service is not distinct, the Company is required to combine that good or service with other promised goods or services until it identifies a bundle of goods or services that is distinct.

The transaction price is then determined and allocated to the identified performance obligations in proportion to their standalone selling prices ("SSP") on a relative SSP basis. SSP is determined at contract inception and is not updated to reflect changes between contract inception and when the performance obligations are satisfied. Determining the SSP for performance obligations requires significant judgment. In developing the SSP for a performance obligation, the Company considers applicable market conditions and relevant entity-specific factors, including factors that were contemplated in negotiating the agreement with the customer and estimated costs. In certain circumstances, the Company may apply the residual method to determine the SSP of a good or service if the standalone selling price is considered highly variable or uncertain. The Company validates the SSP for performance obligations by evaluating whether changes in the key assumptions used to determine the SSP will have a significant effect on the allocation of arrangement consideration between multiple performance obligations.

If the consideration promised in a contract includes a variable amount, the Company estimates the amount of consideration to which it will be entitled in exchange for transferring the promised goods or services to a customer. The Company determines the amount of variable consideration by using the expected value method or the most likely amount method. The Company includes the unconstrained amount of estimated variable consideration in the transaction price. The amount included in the transaction price is constrained to the amount for which it is probable that a significant reversal of cumulative revenue recognized will not occur. At the end of each subsequent reporting period, the Company re-evaluates the estimated variable consideration included in the transaction price and any related constraint, and if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment.

If an arrangement includes development and regulatory milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the Company's control or the licensee's control, such as regulatory approvals, are generally not considered probable of being achieved until those approvals are received.

In determining the transaction price, the Company adjusts consideration for the effects of the time value of money if the timing of payments provides the Company with a significant benefit of financing. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the licensees and the transfer of the promised goods or services to the licensees will be one year or less. The Company assessed its revenue-generating arrangement in order to determine whether a significant financing component exists and concluded that a significant financing component does not exist in the

arrangement. For arrangements with licenses of intellectual property that include sales-based royalties, including milestone payments based on the level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes royalty revenue and sales-based milestones at the later of (i) when the related sales occur, or (ii) when the performance obligation to which the royalty has been allocated has been satisfied.

The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied at a point in time or over time, and if over time this is based on the use of an output or input method.

Recently Issued Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board (“FASB”) issued ASU No. 2016-02, Leases, which will replace the existing guidance in ASC 840, “Leases”, and in July 2018, the FASB issued ASU No. 2018-11, Leases (Topic 842): Targeted Improvements. The new leasing standards generally requires lessees to recognize operating and financing lease liabilities and corresponding right-of-use assets on the consolidated balance sheet and to provide enhanced disclosures surrounding the amount, timing and uncertainty of cash flows arising from leasing arrangements. We will adopt the new standard effective January 1, 2019 and will not restate comparative periods. Presentation of leases within the consolidated statements of operations and consolidated statements of cash flows will be generally consistent with the current lease accounting guidance. We will elect the package of practical expedients permitted under the transition guidance and as such, the adoption of this ASU will not change the classification of any of our leases. We will elect to combine lease and non-lease components, elect not to record leases with an initial term of 12 months or less on the balance sheet and recognize the associated lease payments in the consolidated statements of operations on a straight-line basis over the lease term. We estimate that approximately $45.0 million will be recognized as total lease liabilities and approximately $41.0 million will be recognized as total right-of-use assets on our consolidated balance sheet as of January 1, 2019. Otherwise, we do not expect the new standard to have a material impact on our 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 statements of cash flows. The Company adopted the standard on the required effective date of January 1, 2018. This guidance did not have a significant impact on the Company’s consolidated financial statements and related disclosures.

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 in the statements 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 statements of cash flows. The Company adopted this standard during the first quarter of 2018. Restricted cash is now included as a component of cash, cash equivalents, and restricted cash on the Company’s consolidated statements of cash flows. Restricted cash balances are classified as non-current unless, under the terms of the applicable agreements, the funds will be released from restrictions within one year from the balance sheet date. The inclusion of restricted cash increased the beginning balances of the consolidated statements of cash flows by $0.8 million, $0.6 million and $39,000, respectively, and the ending balances by $2.4 million, $0.8 million and $0.6 million, respectively, for the years ended December 31, 2018, 2017 and 2016.

In May 2017, the FASB issued ASU No. 2017-09, Compensation—Stock Compensation (Topic 718) — Scope of Modification Accounting, which applies to entities that change the terms or conditions of a share-based payment award. The amendments in this standard include guidance on determining whether changes to the terms and conditions of share-based payment awards require an entity to apply modification accounting under Topic 718 unless all of the following conditions are met: (1) the fair value of the modified award is the same as the fair value of the original award immediately before the original award is modified, and if the modification does not affect any of the inputs to the valuation technique that the entity uses to value the award, then the entity is not required to estimate the value immediately before and after the modification; (2) the vesting conditions of the modified award are the same as the vesting conditions of the original award immediately before the original award is modified; and (3) the classification of the modified award as an equity instrument or a liability instrument is the same as the classification of the original award immediately before the original award is modified. The Company adopted the standard on the required effective date of January 1, 2018. This guidance did not have a significant impact on the Company's consolidated financial statements and related disclosures.

In June 2018, the FASB issued ASU 2018-07, Compensation—Stock Compensation (Topic 718) – Improvements to Nonemployee Share-Based Payment Accounting ("ASU 2018-07"), which aligns the accounting for share-based payment awards issued to employees and non-employees. Under the new guidance, the existing guidance regarding employees will apply to share-based transactions with non-employees, as long as the transaction is not effectively a form of financing, with the exception of specific guidance related to the attribution of compensation cost. The cost of non-employee awards will continue to be recorded as if the grantor had paid cash for the goods or services. In addition, the contractual term will be able to be used in lieu of an expected term in the option-pricing model for non-employee awards. The amendments in the new guidance are effective for public entities for fiscal years beginning after December 15, 2018, including interim periods within that fiscal year. Early adoption is permitted, including in interim periods, but no earlier than an entity's adoption of Accounting Standards Codification 606. The Company is in the process of evaluating the impact that this new guidance will have on its consolidated financial statements.

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 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 based on prices obtained from independent pricing sources. Consistent with the fair value hierarchy described above, securities with validated quotes from pricing services are 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, 2018 and 2017:

	December 31, 2018			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Cash equivalents	$190,943	$190,943	$—	$—
Total cash equivalents	190,943	190,943	—	—
Marketable securities:				
U.S. government securities	220,482	—	220,482	—
U.S. corporate bonds	258,566	—	258,566	—
International corporate bonds	78,468	—	78,468	—
U.S. commercial paper	77,611	—	77,611	—
International commercial paper	96,706	—	96,706	—
Total marketable securities	731,833	—	731,833	—
	$922,776	$190,943	$731,833	$—

	December 31, 2017			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Cash equivalents	$306,235	$306,235	$—	$—
Total cash equivalents	306,235	306,235	—	—
Marketable securities:				
U.S. government securities	49,606	—	49,606	—
U.S. corporate bonds	48,959	—	48,959	—
U.S. commercial paper	65,583	—	65,583	—

International commercial paper	48,465	—	48,465	—
Total marketable securities	212,613	—	212,613	—
	$518,848	$306,235	$212,613	$ —

During the years ended December 31, 2018 and 2017, there were no transfers among the Level 1, Level 2 and Level 3 categories.

Marketable Securities

The following tables summarize the gross unrealized gains and losses of the Company's marketable securities as of December 31, 2018 and 2017:

	December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
U.S. government securities	$220,531	$ 8	$ (57)	$220,482
U.S. corporate bonds	258,876	6	(316)	258,566
International corporate bonds	78,600	—	(132)	78,468
U.S. commercial paper	77,630	8	(27)	77,611
International commercial paper	96,711	8	(13)	96,706
	$732,348	$ 30	$ (545)	$731,833

	December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
U.S. government securities	$49,612	$ —	$ (6)	$49,606
U.S. corporate bonds	48,982	2	(25)	48,959
U.S. commercial paper	65,583	—	—	65,583
International commercial paper	48,465	—	—	48,465
	$212,642	$ 2	$ (31)	$212,613

As of December 31, 2018, all marketable securities, except for two U.S. corporate bonds, held by the Company had remaining contractual maturities of one year or less.

As of December 31, 2018 and 2017, the Company held 145 and 11 marketable securities, respectively, that were in a loss position for less than one year due to fluctuations in interest rates.

There have been no impairments of the Company's assets measured and carried at fair value during the years ended December 31, 2018 and 2017.

4. Balance Sheet Components

Property and Equipment, net

Property and equipment, net consists of the following:

	December 31,	
	2018	2017
	(in thousands)	
Computer hardware and software	$2,148	$1,090
Furniture and equipment	1,002	1,029
Leasehold improvements	4,709	2,967
	7,859	5,086
Less: Accumulated depreciation	(2,216)	(1,073)
	$5,643	$4,013

Depreciation expense for the years ended December 31, 2018, 2017 and 2016 was $1.1 million, $0.5 million and $0.3 million, respectively.

The useful life for computer hardware and software is three years, furniture and equipment is five years and leasehold improvements is the lesser of the useful life or the term of the respective lease.

Accrued Expenses

Accrued expenses consist of the following:

	December 31,	
	2018	2017
	(in thousands)	
Development costs	$21,216	$23,473
Employee-related expenses	19,638	15,838
Professional services	10,903	3,166
Other accrued expenses	237	124
	$51,994	$42,601

5. Commitments and Contingencies

Operating Leases

The Company leases office space in two multi-tenant buildings in Cambridge, Massachusetts, consisting, as of December 31, 2018, of 58,442 square feet in the first building under an operating lease that will expire on August 31, 2024 and 19,805 square feet in the second building under an operating lease that will expire on August 31, 2024.

In April 2018, the Company entered into the First Amendment to the lease for office space in the second multi-tenant building and thereby increased the amount of square feet of office space from 19,805 square feet to 40,419 square feet, an increase of 20,614 square feet, consisting of (i) 13,481 square feet that began on August 1, 2018, and (ii) 7,133 square feet that began on October 1, 2018. The term for this additional space will expire on August 31, 2024. Additionally, the term of the existing lease was extended from February 28, 2022 until August 31, 2024.

In May 2018, the Company entered into a lease for office space in a multi-tenant building in Raleigh, North Carolina. The amount of square feet of office space is 15,525 square feet and the lease period began on September 1, 2018. The term for this space will expire on November 30, 2024.

In October 2018, the Company entered into the Seventh Amendment to the lease for office space in the first building and thereby increased the amount of square feet of office space from 54,943 square feet to 58,442 square feet. The increase of 3,499 square feet began on December 1, 2018. The term for this additional space will expire on August 31, 2024.

In December 2018, the Company entered into a lease in a third multi-tenant building in Cambridge, Massachusetts, for 15,975 square feet of office space which will begin on March 1, 2019. The term for this lease will expire on February 28, 2024.

Rent expense for the years ended December 31, 2018, 2017 and 2016, was $6.5 million, $3.7 million, and $2.0 million, respectively.

Future minimum lease payments under non-cancelable operating leases are as follows at December 31, 2018:

Years Ending December 31,	(in thousands)
2019	$ 7,918
2020	8,299
2021	8,463
2022	8,692
2023	8,894
Thereafter	5,415
	$ 47,681

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 brexanolone and the Company’s compound known as 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 of December 31, 2018, the Company has paid to CyDex $1.0 million for licensing fees, which was recorded as research and development expense.

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 brexanolone; 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 brexanolone; 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. As of December 31, 2018, the Company has recorded research and development expense and made cash payments of $2.3 million related to these clinical development and regulatory milestones.

For the year ended December 31, 2016, additional clinical development milestones were met for the brexanolone 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, 2017, the Company did not record any expense or make any milestone payments related to clinical development or regulatory milestones for the brexanolone program under the license agreement with CyDex.

For the year ended December 31, 2018, additional clinical development milestones were met for the brexanolone program under the license agreement with CyDex, and accordingly, the Company recorded research and development

expense and made cash payments totaling $0.8 million.

University of California License Agreements

In October 2013, the Company entered into a non-exclusive license agreement with The Regents of the University of California under which the Company was granted a non-exclusive license to certain clinical data and clinical material related to brexanolone for use in the development and commercialization of biopharmaceutical products in the licensed field, including status epilepticus and postpartum 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. As of December 31, 2015, the Company paid to The Regents of the University of California clinical development milestones of $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 developed using the data and materials. 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.

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. As of December 31, 2018, the Company has recorded research and development expense and made cash payments of $0.3 million related to these regulatory and sales milestones.

For the years ended December 31, 2017 and 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.

For the year ended December 31, 2018, the Company recorded research and development expense and made cash payments of $0.2 million related to regulatory milestones under the license agreements with The Regents of the University of California.

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. As of December 31, 2018, the Company has recorded research and development expense and made a cash payment of $50,000 related to these clinical and development milestones.

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 years ended December 31, 2018, 2017 and 2016, the Company did not record any expense or make any milestone payments under the license agreement with Washington University.

Consulting Agreement

In January 2014, the Company entered into a consulting agreement with a then 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. As of December 31, 2018, the Company recorded research and development expense of $1.8 million, comprised of $0.5 million in cash and $1.3 million related to the issuance of 39,681 shares of the Company's common stock, related to the achievement of these milestones.

For the years ended December 31, 2018, 2017 and 2016, the Company did not record any expense or make any milestone payments under the consulting agreement with the non-employee advisor.

6. Collaboration Agreement

Effective June 12, 2018, the Company entered into a strategic collaboration with Shionogi & Co., Ltd., ("Shionogi") for the clinical development and commercialization of SAGE-217 for the treatment of major depressive disorder ("MDD") and other potential indications in Japan, Taiwan and South Korea.

Under the terms of the agreement, Shionogi will be responsible for all clinical development, regulatory filings and commercialization of SAGE-217 for MDD, and potentially other indications, in Japan, Taiwan and South Korea. Shionogi was required to make an upfront payment to the Company of $90.0 million, and the Company will be eligible to receive additional payments of up to $485.0 million if certain regulatory and commercial milestones are achieved by Shionogi. The potential future milestone payments include up to $70.0 million for the achievement of specified regulatory milestones, up to $30.0 million for the achievement of specified commercialization milestones, and up to $385.0 million for the achievement of specified net sales milestones. Due to the uncertainty of pharmaceutical development and the high historical failure rates generally associated with drug development, the Company may not receive any additional milestone payments or any royalty payments from Shionogi. The Company will receive tiered royalties on sales of SAGE-217 in Japan, Taiwan and South Korea, if development efforts are successful, with tiers averaging in the low to mid-twenty percent range, subject to other terms of the agreement. Shionogi has also granted to the Company certain rights to co-promote SAGE-217 in Japan. The Company maintains exclusive rights to develop and commercialize SAGE-217 outside of Japan, Taiwan and South Korea. The upfront cash payment and any payments for milestones and royalties are non-refundable, non-creditable and not subject to set-off.

The Company concluded that Shionogi meets the definition to be accounted for as a customer since the Company is delivering intellectual property and know-how rights for the SAGE-217 program in support of territories in which the parties are not jointly sharing the risks and rewards. In addition, the Company determined that the Shionogi collaboration met the requirements to be accounted for as a contract, including that it was probable that the Company will collect the consideration related to the up-front payment to which the Company was entitled in exchange for the goods or services that will be delivered to Shionogi.

In determining the appropriate amount of revenue to be recognized under ASC 606, the Company performed the following steps: (i) identified the promised goods or services in the contract; (ii) determined whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measured the transaction price, including the constraint on variable consideration; (iv) allocated the transaction price to the performance obligations; and (v) recognized revenue when (or as) the Company satisfies each performance obligation.

The Company determined that the performance obligations included the license to SAGE-217, supply of certain clinical materials and manufacturing supply of the active pharmaceutical ingredient ("API"). The performance

obligation related to the license to SAGE-217 was determined to be distinct from other performance obligations and therefore was a standalone performance obligation for which control was transferred upon signing. The obligation to provide certain clinical materials was determined to be a separate performance obligation. The agreement related to supplying API was determined to be an option for Shionogi to purchase, rather than a firm obligation since no minimum amount or quantities are specified and therefore, was not considered a performance obligation within the main agreement. Given this fact pattern, the Company has concluded the agreement has two performance obligations.

The Company completed the evaluation of the standalone selling prices of each of the performance obligations and determined that the standalone selling price of the license performance obligation was $90.0 million. The Company recognized the transaction price allocated to the license performance obligation of $90.0 million as revenue during the quarter upon delivery of the license to Shionogi and resulting ability of Shionogi to use and benefit from the license. The remaining transaction price related to the performance obligation for the supply of certain clinical material is not significant. The potential milestone payments that the Company is eligible to receive were excluded from the transaction price, as all milestone amounts were fully constrained based on the probability of achievement. The Company will reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and, if necessary, adjust its estimate of the transaction price.

7. Preferred Stock

The Board of Directors of the Company is authorized, without action by the stockholders, to designate and issue up to an aggregate of 5,000,000 shares of preferred stock in one or more series. The Board of Directors of the Company can designate the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. The Board of Directors of the Company may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of common stock. As of December 31, 2018 and 2017, the Company had no shares of preferred stock issued or outstanding and preferred stock was classified as stockholders' equity.

8. Common Stock

As of December 31, 2018 and 2017, the Company 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, 2018 and 2017, no dividends have been declared.

During the year ended December 31, 2018, the Company received 2,073 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, 2018 was $211,000.

During the year ended December 31, 2017, the Company received 614 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, 2017 was $113,000.

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.

9. Stock-Based Compensation

Restricted Stock Units

During the year ended December 31, 2017, the Company granted 32,500 restricted stock units to employees of the Company. The Company did not grant restricted stock units prior to January 1, 2017. These restricted stock units vest ratably over two years, with cliff vesting of 50% at both the one-year and two-year anniversary of the grant date, which was in February 2018 and will be in February 2019, respectively.

During the year ended December 31, 2018, the Company granted 71,400 performance restricted stock units to employees of the Company. 33,600 performance restricted stock units will vest upon the achievement of a certain regulatory milestone; in one case, upon meeting the milestone and, in the other case, upon the first anniversary of achievement of the milestone. 37,800 performance restricted stock units will vest upon the achievement of a certain commercial milestone.

The fair value of restricted stock units that vested during the year ended December 31, 2018 was $2.6 million. No restricted stock units vested during the year ended December 31, 2017.

The table below summarizes activity relating to restricted stock units:

	Shares
Outstanding as of December 31, 2017	29,100
Granted	71,400
Vested	(14,550)
Forfeited	(3,250)
Outstanding as of December 31, 2018	82,700

Stock Option Plans

On July 2, 2014, the stockholders of the Company approved the 2014 Stock Option and Incentive Plan (the "2014 Stock Option Plan"), which became effective immediately prior to the completion of the Company's 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 no longer grants 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.

The 2014 Stock Option Plan provides for an annual increase, to be added on the first day of each fiscal year, of up to 4% of the Company's outstanding shares of common stock as of the last day of the prior year. On January 1, 2019, 1,875,530 shares of common stock, representing 4% of the Company's outstanding shares of common stock as of December 31, 2018, were added to the 2014 Stock Option Plan.

On December 15, 2016, the Board of Directors of the Company (the "Board") approved the 2016 Inducement Equity Plan (the "2016 Stock Option Plan"). The 2016 Stock Option Plan provides for the grant of equity awards to individuals who have not previously been an employee or a non-employee director of the Company to induce them to accept employment and to provide them with a proprietary interest in the Company. On September 20, 2018, the Board amended the 2016 Stock Option Plan to increase the total number of shares reserved for issuance under such plan by 1,200,000 shares.

Terms of restricted stock awards, restricted stock units, and stock options, including vesting requirements, are determined by the Board or the Compensation Committee of the Board, subject to the provisions of the applicable stock option plan. Options 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 25% cliff vesting at the one-year anniversary. All option awards expire in 10 years.

During the years ended December 31, 2018, 2017, 2016 and 2015, the Company granted 524,003, 449,208, 74,039 and 497,100 options, respectively, to employees to purchase shares of common stock that contain performance-based vesting criteria, primarily related to the achievement of certain clinical and regulatory development milestones related to product candidates and commercial milestones. 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, which consider the inherent risk and uncertainty regarding the future outcomes of the activities described by the milestones.

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.

During the year ended December 31, 2018, a performance milestone was achieved under a stock option granted to a consultant. The milestone was related to the consummation of a licensing or corporate partnering arrangement. During the year ended December 31, 2018, the Company recognized stock-based compensation expense related to this milestone of $6.9 million.

During the year ended December 31, 2018, one milestone was achieved. This milestone represents 33% of the performance-based option grants that were made during the year ended December 31, 2017. During the year ended December 31, 2018, the Company recognized stock-based compensation expense related to this milestone of $4.4 million.

During the year ended December 31, 2018, the remaining milestone for the performance-based option grants that were made during the years ended December 31, 2016 and December 31, 2015 was not met, and accordingly, those options were cancelled. They represented 50% and 35% of the performance-based option grants that were made during the years ended December 31, 2016 and December 31, 2015, respectively. The Company recognized no stock-based compensation expense related to this milestone.

As of December 31, 2018, for grants that are outstanding, the achievement of the milestones that had not been met that are the criteria for vesting of performance-based stock options was considered not probable, and therefore no expense has been recognized related to these awards for the year ended December 31, 2018.

Stock-based compensation expense for stock options, restricted stock units and the employee stock purchase plan recognized during the years ended December 31, 2018, 2017 and 2016 was as follows:

	2018	2017	2016
	(in thousands)		
Research and development	$50,871	$19,893	$11,197
General and administrative	51,092	15,641	11,823
	$101,963	$35,534	$23,020

Stock-based compensation expense by award type recognized during the years ended December 31, 2018, 2017 and 2016 was as follows:

	2018	2017	2016
	(in thousands)		
Stock options	$100,342	$34,525	$22,820
Restricted stock units	651	617	—
Employee stock purchase plan	970	392	166
Restricted stock awards	—	—	34
	$101,963	$35,534	$23,020

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 of stock options granted under the Company's stock option plans during the years ended December 31, 2018, 2017 and 2016 was $109.92, $41.94 and $24.97, respectively.

The fair value of each option granted to employees and non-employee directors during the years ended December 31, 2018, 2017 and 2016 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,		
	2018	2017	2016
Expected dividend yield	0 %	0 %	0 %
Expected volatility	74.45 %	79.89 %	80.15 %
Risk-free interest rate	2.68 %	2.03 %	1.47 %
Expected life of option	6.04 years	6.03 years	6.05 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, 2018, 2017 and 2016, the weighted-average forfeiture rates were 10.7%, 13.3% and 9.6%, respectively.

For options granted to non-employees, the expected term 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	Weighted Average Remaining Life	Aggregate Intrinsic Value

		Price	(in years)	(in thousands)
Outstanding as of December 31, 2017	5,586,593	$ 43.58	8.09	$ 676,717
Granted	3,103,494	164.50		
Exercised	(767,147)	34.67		
Forfeited	(392,173)	64.74		
Outstanding as of December 31, 2018	7,530,767	$ 93.22	8.03	$ 227,447
Vested and expected to vest as of December 31, 2018	6,254,429	$ 85.55	7.86	$ 209,356
Exercisable as of December 31, 2018	2,846,158	$ 40.69	6.71	$ 159,799

At December 31, 2018, the Company had unrecognized stock-based compensation expense related to its unvested service-based stock option awards of $282.6 million, which is expected to be recognized over the remaining weighted average vesting period of 2.88 years.

At December 31, 2018, 772,347 performance-based stock options were both outstanding and unvested, and the total unrecognized stock-based compensation expense related to those awards was $50.1 million.

The intrinsic value of stock options exercised during the years ended December 31, 2018, 2017 and 2016 was $98.3 million, $77.7 million and $4.6 million, respectively.

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, 2018, 49,756 shares have been issued under this plan and 232,244 shares are available for issuance under this plan. At December 31, 2018, accrued expenses includes $0.5 million of stock-based compensation expense related to an enrollment period for which the related shares had not been issued as of December 31, 2018.

Shares Reserved and Available for Future Issuance

As of December 31, 2018, the total number of shares reserved under all equity plans, consisting of the 2011 Stock Option Plan, the 2014 Stock Option Plan, the 2014 Employee Stock Purchase Plan and the 2016 Stock Option Plan, is 9,945,522, and 2,332,055 shares were available for issuance under such plans.

10. Net Loss Per Share

Basic and diluted net loss per share was calculated as follows for the years ended December 31, 2018, 2017 and 2016:

	Year ended December 31,		
	2018	2017	2016
Basic net loss per share:			
Numerator:			
Net loss (in thousands)	$(372,882)	$(270,120)	$(158,987)
Denominator:			
Weighted average common stock outstanding - basic	46,121,194	38,113,678	33,492,795
Dilutive effect of shares of common stock equivalents resulting from common stock options and restricted stock units	—	—	—
Weighted average common stock outstanding - diluted	46,121,194	38,113,678	33,492,795
Net loss per share—basic and diluted	$(8.08)	$(7.09)	$(4.75)

The following common stock equivalents outstanding as of December 31, 2018, 2017 and 2016 were excluded from the calculation of diluted net loss per share for the periods presented because including them would have been anti-dilutive:

	Year ended December 31,		
	2018	2017	2016
Stock options	6,758,420	4,915,956	3,985,935
Restricted stock units	13,500	29,100	—
Employee stock purchase plan	16,398	11,683	6,784
	6,788,318	4,956,739	3,992,719

Stock options and restricted stock units that are outstanding and contain performance-based vesting criteria for which the performance conditions have not been met are excluded from the calculation of common stock equivalents outstanding.

11. Income Taxes

There is no current or deferred 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 the U.S. statutory rate to the Company's effective tax rate is as follows:

	Year Ended December 31,		
	2018	2017	2016
Tax due at statutory rate	21.0 %	34.0 %	34.0 %
State taxes, net of federal	6.0	5.1	4.2
Stock-based compensation	2.5	6.4	(1.0)
Foreign rate differential	(4.3)	(3.2)	(3.1)
Federal and state credits	2.5	7.2	10.3
Change in valuation allowance	(27.6)	(22.5)	(41.5)
Other	(0.1)	—	—
Federal and state rate change	—	(24.6)	—
Research and orphan drug credit addback	—	(2.4)	(2.9)
	0.0 %	0.0 %	0.0 %

Significant components of the Company's net deferred tax asset at December 31, 2018 and 2017 are as follows:

	December 31,	
	2018	2017
	(in thousands)	
Net operating losses	$206,460	$131,151
Capitalized start-up costs	1,242	1,362
Tax credit carryforwards	63,653	54,523
Accrued expenses	4,498	3,057
Depreciation and amortization	1,001	685
Stock options	30,925	13,573
Others	568	1,090
Total net deferred tax asset before valuation allowance	308,347	205,441
Valuation allowance	(308,347)	(205,441)
Net deferred tax asset	$—	$—

As of December 31, 2018, the Company had federal and state net operating loss carryforwards of $755.0 million and $760.7 million, respectively, which begin to expire in 2031 and 2030, respectively. As of December 31, 2018, the Company had federal and state research and development tax credits carryforwards of $20.3 million and $4.1 million, respectively, which begin to expire in 2031 and 2027, respectively. As of December 31, 2018, the Company had federal orphan drug tax credit carry forwards of $40.0 million, which begin to expire in 2034.

On December 22, 2017, the President of the United States signed into law the Tax Cuts and Jobs Act ("The TCJA"). This legislation reduced the U.S. corporate tax rate from the existing rate of 34% to 21% for tax years beginning after December 31, 2017. As a result of the enacted law, the Company was required to revalue deferred tax assets and liabilities existing as of December 31, 2017 from the 34% federal rate in effect through the end of 2017, to the new 21% rate. This revaluation resulted in a reduction to the Company's deferred tax asset of $66.4 million as of December 31, 2017. This amount was offset by a corresponding reduction to the Company's valuation allowance. The other provisions of the TCJA did not have a material impact on the December 31, 2017 consolidated financial statements. Our final determination of the TCJA impact and the remeasurement of our deferred assets and liabilities was completed prior to the deadline of one year from the enactment of the TCJA. For the year ended December 31, 2018, there were no material changes to our analysis originally performed as of December 31, 2017.

As of December 31, 2018, net deferred tax assets increased approximately $102.9 million, primarily due to the operating loss, timing differences related to stock-based compensation 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 $308.3 million and $205.4 million has been established at December 31, 2018 and 2017, respectively.

Pursuant to Section 382 of the Internal Revenue Code, and similar state tax law, 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 completed a detailed Section 382 study during 2017 on its Net Operating Losses and Credits incurred from the year it began operations in 2011 through December 31, 2016. Based on the study, the Company underwent two ownership changes for Section 382 purposes which occurred on March 11, 2014 and December 31, 2015. As a result of the ownership changes, all of the Company's NOL and Tax Credit carryforwards as of the ownership change dates are subject to limitation under Section 382. Any NOLs or Tax Credits generated after the December 2015 change are not subject to this annual limitation. However, subsequent ownership changes, as defined by Section 382, may potentially further limit the amount of net operating loss carryforwards that could be utilized to offset future taxable income.

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,		
	2018	2017	2016
	(in thousands)		
Unrecognized tax benefits—as of the beginning of the year	$ —	$ —	$ —
Gross increases—current period tax positions	—	—	—
Gross decreases—tax positions of prior periods	—	—	—
Unrecognized tax benefits—as of the end of the year	$ —	$ —	$ —

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, 2018 and 2017, 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 2015 to the present. The tax attributes prior to 2015 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.

12. Employee Benefit Plan

The Company maintains a 401(k) profit sharing plan (the "Plan") for its employees. Each employee may elect to contribute a portion of his or her compensation to the Plan, subject to annual limits established by the Internal Revenue Service. For the years ended December 31, 2018, 2017 and 2016, the Company matched 50% of eligible contributions up to 6% of employee contributions. For the years ended December 31, 2018, 2017 and 2016 the Company contributed $1.8 million, $0.9 million and $0.4 million, respectively.

13. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2018 and 2017. 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.

	2018 First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share amounts)				
Total revenue	$—	$90,000	$—	$273	$90,273
Total operating expenses	78,119	112,147	128,745	164,500	483,511
Loss from operations	(78,119)	(22,147)	(128,745)	(164,227)	(393,238)
Net loss	(74,598)	(16,978)	(122,918)	(158,388)	(372,882)
Net loss per share—basic and diluted	$(1.68)	$(0.36)	$(2.63)	$(3.38)	$(8.08)

	2017 First Quarter	Second Quarter	Third Quarter	Fourth Quarter	Total
	(in thousands, except per share amounts)				
Total revenue	$—	$—	$—	$—	$—
Total operating expenses	57,480	70,854	74,373	70,448	273,155
Loss from operations	(57,480)	(70,854)	(74,373)	(70,448)	(273,155)
Net loss	(56,778)	(70,202)	(73,719)	(69,421)	(270,120)
Net loss per share—basic and diluted	$(1.52)	$(1.88)	$(1.97)	$(1.75)	$(7.09)

Exhibit Index

Exhibit No.	Description
3.1	Fifth Amended and Restated Certificate of Incorporation of the Registrant, as currently in effect (incorporated by reference to Exhibit 3.1 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 3.2 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 10.2 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 (File No. 333-196849) filed on July 8, 2014)

Exhibit No.	Description
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)
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)

Exhibit No.	Description
10.31	Sixth Amendment to Lease by and between ARE-MA Region No. 38, LLC and the Registrant, dated as of May 8, 2017 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 3, 2017)
10.32+	2014 Employee Stock Purchase Plan, dated June 7, 2017 (incorporated by reference to Exhibit 10.2 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 3, 2017)
10.33+	Offer Letter by and between the Registrant and Michael Cloonan, dated March 21, 2017 (incorporated by reference to Exhibit 10.3 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 3, 2017)
10.34+	Severance and Change In Control Agreement between the Registrant and Michael Cloonan, dated March 21, 2017 (incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on August 3, 2017)
10.35	First Amendment to Lease by and between CLPF-Cambridge Science Center LLC and the Registrant dated April 4, 2018 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36544) filed on May 5, 2018)
10.36+	Amended and Restated 2016 Inducement Equity Plan and forms of agreements thereunder, as amended and restated on September 20, 2018 (incorporated by reference to Exhibit 10.1 of the Registration's Quarterly Report on Form 10-Q (File No. 001-36544) filed on November 6, 2018)
10.37+	Amended and Restated Non-Employee Director Compensation Policy, dated as of September 20, 2018 (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, 2018)
10.38	Seventh Amendment to Lease by and between ARE-MA Region No. 38, LLC and the Registrant, dated October 23, 2018 (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, 2018)
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.

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 19, 2019 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 19, 2019
/s/ Kimi Iguchi Kimi Iguchi	Chief Financial Officer (Principal Financial and Accounting Officer)	February 19, 2019
/s/ Michael F. Cola Michael F. Cola	Director	February 19, 2019
/s/ Steven Paul Steven Paul, M.D.	Director	February 19, 2019
/s/ Kevin P. Starr Kevin P. Starr	Director	February 19, 2019
/s/ James Frates James Frates	Director	February 19, 2019
/s/ Geno Germano Geno Germano	Director	February 19, 2019
/s/ Asha Nayak Asha Nayak	Director	February 19, 2019
/s/ Elizabeth Barrett Elizabeth Barrett	Director	February 19, 2019

/s/ George Golumbeski George Golumbeski, Ph.D.	Director	February 19, 2019

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