Sage Therapeutics, Inc.
Form 424B5
February 07, 2018
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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-208870

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion

Preliminary prospectus supplement dated February 7, 2018

Prospectus supplement

(To prospectus dated January 5, 2016)

$575,000,000

Common stock

We are selling up to $575,000,000 of our common stock in this offering.

Our common stock is traded on The Nasdaq Global Market under the symbol SAGE. On February 6, 2018, the last reported sale price of our common stock was $179.90 per share, as reported on The Nasdaq Global Market.

Investing in our common stock involves risks. See Prospectus Supplement Summary Risks Related to Our Business beginning on page S-14 of this prospectus supplement and Risk Factors beginning on page S-20 of this prospectus supplement and in our Annual Report on Form 10-K for the year ended December 31, 2016 and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, which are incorporated herein by reference.

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

	Per share	Total
Public offering price	$	$
Underwriting discounts and commissions(1)	$	$
Proceeds, before expenses, to Sage Therapeutics, Inc.	$	$

(1) We have agreed to reimburse the underwriters for certain FINRA-related expenses. See Underwriting.
We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to approximately $86,250,000 of additional shares of our common stock at the public offering price, less the underwriting discount.

The underwriters expect to deliver the shares of common stock against payment to the investors on or about , 2018.

J.P. Morgan **Goldman Sachs & Co. LLC** **Morgan Stanley**

The date of this prospectus supplement is , 2018.

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Prospectus supplement

Prospectus

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About this prospectus supplement

This document is part of the registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a shelf registration process and consists of two parts. The first part is this prospectus supplement, including the documents incorporated by reference, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference, gives more general information, some of which may not apply to this offering. Generally, when we refer to the prospectus, we are referring to both parts combined. This prospectus supplement may add to, update or change information in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement or the accompanying prospectus.

If information in this prospectus supplement is inconsistent with the accompanying prospectus or with any document incorporated by reference that was filed with the SEC before the date of this prospectus supplement, you should rely on this prospectus supplement. This prospectus supplement, the accompanying prospectus and the documents incorporated by reference into each include important information about us, the securities being offered and other information you should know before investing in our securities. You should also read and consider information in the documents we have referred you to in the sections of this prospectus supplement entitled Where You Can Find Additional Information and Incorporation of Certain Information by Reference and in the sections of the accompanying prospectus entitled Where You Can Find Additional Information and Incorporation of Certain Information by Reference.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We take no responsibility for, and can provide no assurances as to the reliability of, any information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We are not offering to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than as of the date of this prospectus supplement or the accompanying prospectus, as the case may be, or in the case of the documents incorporated by reference, the date of such documents, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of our securities. Our business, financial condition, liquidity, results of operations and prospects may have changed since those dates.

All references in this prospectus supplement or the accompanying prospectus to the Company, we, us, or our mean Sage Therapeutics, Inc. and our subsidiaries, unless we state otherwise or the context otherwise requires. We own various U.S. federal trademark applications and unregistered trademarks, including our corporate logo. This prospectus supplement and the information incorporated herein by reference contain references to trademarks, service marks and trade names owned by us or other companies. Solely for convenience, trademarks, service marks and trade names referred to in this prospectus supplement and the information incorporated herein, including logos, artwork, and other visual displays, may appear without the ® or symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks, service marks and trade names.

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We do not intend our use or display of other companies trade names, service marks or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus supplement or any related free writing prospectus are the property of their respective owners.

No action is being taken in any jurisdiction outside the United States to permit a public offering of the securities or possession or distribution of this prospectus supplement or the accompanying prospectus in that jurisdiction. Persons who come into possession of this prospectus supplement or the accompanying prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement or the accompanying prospectus applicable to that jurisdiction.

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Where you can find additional information; incorporation by reference

We have filed with the SEC a registration statement on Form S-3 under the Securities Act of 1933, as amended, or the Securities Act, with respect to the common stock offered by this prospectus supplement. This prospectus supplement, filed as part of the registration statement, does not contain all the information set forth in the registration statement and its exhibits and schedules, portions of which have been omitted as permitted by the rules and regulations of the SEC. For further information about us, we refer you to the registration statement and to its exhibits and schedules.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any materials we file at the SEC s Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information about the Public Reference Room. The SEC also maintains a website at www.sec.gov that contains periodic and current reports, proxy and information statements, and other information regarding registrants that are filed electronically with the SEC.

These documents are also available, free of charge, through the Investors & Media section of our website, which is located at www.sagerx.com. Information contained on our website is not incorporated by reference into this prospectus supplement or the accompanying prospectus and you should not consider information on our website to be part of this prospectus supplement or the accompanying prospectus.

The SEC allows us to incorporate by reference the information and reports we file with it, which means that we can disclose important information to you by referring you to these documents. The information incorporated by reference is an important part of this prospectus supplement and accompanying prospectus, and information that we file after the date hereof with the SEC will automatically update and supersede the information already incorporated by reference. We are incorporating by reference the documents listed below, which we have already filed with the SEC, and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities and Exchange Act of 1934, as amended, or the Exchange Act, except as to any portion of any future report or document that is not deemed filed under such provisions, after the date of this prospectus supplement and prior to the termination of this offering:

- Annual Report on Form 10-K for the year ended December 31, 2016, as filed with the SEC on February 24, 2017;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2016 from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed), which was filed with the SEC on April 28, 2017;
- Quarterly Reports on Form 10-Q filed with the SEC for the quarters ended March 31, 2017, June 30, 2017 and September 30, 2017, as filed with the SEC on May 10, 2017, August 3, 2017 and November 2, 2017, respectively;
- Current Reports on Form 8-K filed with the SEC on March 9, 2017, June 8, 2017, September 12, 2017, November 8, 2017, November 9, 2017, November 15, 2017, November 17, 2017, December 7, 2017, January 8, 2018, January 31, 2018 and February 7, 2018 (in each case, except for information contained therein which is furnished rather than filed); and
- The description of our common stock contained in our registration statement on Form 8-A, which was filed with the SEC on July 15, 2014, including any amendment or report filed for the purpose of updating such description.

Upon request, we will provide, without charge, to each person, including any beneficial owner, to whom a copy of this prospectus is delivered a copy of the documents incorporated by reference into

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this prospectus. You may request a copy of these filings, and any exhibits we have specifically incorporated by reference as an exhibit in this prospectus, at no cost by writing or telephoning us at the following:

Sage Therapeutics, Inc., 215 First Street, Cambridge, Massachusetts, 02142, Attention: Secretary, (617) 299-8380.

You may also access these documents, free of charge, on the SEC s website at *www.sec.gov* or on our website at *www.sagerx.com*. Information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information on, or that can be accessed from, our website as part of this prospectus supplement or the accompanying prospectus.

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Special note regarding forward-looking statements

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein contain statements that are not historical facts and are considered forward-looking within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. These forward-looking statements contain projections about the advancement and potential of our product candidates, our future results of operations or our financial position and other plans and expectations with respect to our activities. In some cases you can identify these statements by forward-looking words such as anticipate, believe, could, continue, estimate, expect, intend, may, should, will, projected or the negative of such words or other similar words or phrases. We believe that it is important to communicate our future expectations to our investors. However, there may be events in the future that we are not able to accurately predict or control, and that may cause our actual results to differ materially from the expectations we describe in our forward-looking statements.

Investors are cautioned not to unduly rely on forward-looking statements because these statements are based on the beliefs and assumptions of our management based on information currently available to management and they relate to future events or our future financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our plans and expectations with respect to development and potential commercialization of our product candidates in the central nervous system disorders we discuss in this prospectus supplement, and potentially in other indications;
- our ability, within the expected timeframes, to file a new drug application with the U.S. Food and Drug Administration and a possible marketing authorization application with the European Medicines Agency seeking approval to market our proprietary intravenous, or IV, formulation of brexanolone as a treatment for postpartum depression, and our expectations as to the sufficiency of the data generated from our clinical trials and non-clinical studies to support regulatory approval;
- our expectations as to the timing of a potential launch of brexanolone IV in the United States to treat PPD, and our views as to our future readiness for such a launch;
- 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 or future clinical trials;
- our expectations with respect to the anticipated regulatory approval requirements and review pathway for our product candidates and the potential to obtain regulatory approval and to commercialize any product, if approved;
- our estimates regarding expenses; use of cash; timing of future cash needs; and capital requirements;
- our potential to achieve future revenues;
- our expectations as to the market, pricing and reimbursement environment for our potential products, and the potential for future revenues;
- our expectations with respect to the availability of supplies of our product candidates, and the expected performance of our third-party manufacturers;

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our expectations with respect to the performance of our contract research organizations and other third parties whose activities are important to our development and future commercialization efforts;

our ability to obtain and maintain intellectual property protection for our proprietary assets and other forms of exclusivity relevant to our business;

the estimated number of patients in indications of interest to us; the potential for our product candidates in those indications, if approved; the size of the potential markets for our product candidates; and our ability to serve those markets;

the anticipated rate and degree of market acceptance, and expectations regarding pricing and the potential scope, level and availability of reimbursement, of our product candidates in any indication and in any country if approved;

our plans for expanding our activities, including outside the United States, and the potential for future collaborations and other types of contractual relationships, if appropriate, for accomplishing our strategic objectives;

the level of costs we may incur in connection with our activities, the possible timing and sources of future financings, and our ability to obtain additional financing when needed 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 in the future pursue;

the potential risk of loss of key scientific or management personnel; and

other risks and uncertainties, including those listed under the Risk Factors section.

These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those indicated by these forward-looking statements, including, without limitation: the risk that regulatory authorities may, despite prior advice, decide that the clinical and nonclinical data from our brexanolone development program in postpartum depression are not sufficient to support a filing for regulatory approval or do not support the grant of regulatory approval, and may require additional trials, analyses or data; the risk that issues may arise during inspections by regulatory authorities of our facilities, data and systems or those of our contract research organization, contract manufacturer or clinical sites that could delay or prevent us from gaining approval of brexanolone; the possibility that we may experience slower than expected clinical site initiation or slower than expected identification and enrollment of evaluable patients in our ongoing or future clinical trials; the potential for delays or problems in analyzing data or the need for additional analysis, data or patients; the potential that future nonclinical and clinical results may not be positive and may not support further development of our product candidates; the potential for unexpected adverse events or other safety or tolerability issues arising in the conduct of our clinical trials or nonclinical studies to impact our ability to continue clinical trials or further development of the applicable product candidate or to gain regulatory approval; the risk that our estimates of the prevalence of the diseases for which we are developing our product candidates may be significantly lower than we expect; the risk that internal and external costs required for our activities, and to build our organization, and the resulting use of cash, may be higher than we expect, or we may conduct additional clinical trials or pre-clinical studies, or engage in new activities, requiring additional expenditures and using cash more quickly than anticipated; the risk that even if brexanolone or any of our other product candidates is approved, we may not be able to obtain pricing, reimbursement or market acceptance at the levels we expect; and the risk that we may encounter other unexpected hurdles or issues in the development, manufacture and potential future commercialization of our product candidates that may impact our timing, progress or results, as well as those risks more fully

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discussed in the Risk Factors section and under Risks Related to Our Business in this prospectus supplement, the section of the accompanying prospectus entitled Risk Factors and the risk factors and cautionary statements described in other documents that we file from time to time with the SEC, specifically under Item 1A: Risk Factors and elsewhere in our most recent Annual Report on Form 10-K for the year ended December 31, 2016, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K.

Given these uncertainties, readers should not place undue reliance on our forward-looking statements. These forward-looking statements speak only as of the date on which the statements were made and are not guarantees of future performance. Except as may be required by applicable law, we do not undertake or intend to update any forward-looking statements after the date of this prospectus supplement or the respective dates of documents incorporated by reference herein or therein that include forward-looking statements.

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Prospectus supplement summary

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary may not contain all the information that you should consider before investing in our securities. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under Risk Factors beginning on page S-20 of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision. This prospectus supplement may add to, update or change information in the accompanying prospectus.

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, brexanolone (USAN) for intravenous, or IV, use, is a proprietary formulation of allopregnanolone, a naturally occurring neuroactive steroid that acts as a positive allosteric modulator of $GABA_A$ receptors, including both synaptic and extrasynaptic populations. We are currently developing brexanolone as a potential treatment for postpartum depression, or PPD. In November 2017, we announced positive top-line data from our Hummingbird program: two placebo-controlled Phase 3 clinical trials of brexanolone IV, one evaluating patients with severe PPD and one evaluating patients with moderate PPD. Both trials achieved their primary endpoints. We believe these results, together with the results of prior clinical studies of brexanolone IV in PPD and nonclinical studies, will be sufficient to support the submission of a New Drug Application, or NDA, to the U.S. Food and Drug Administration, or FDA, seeking approval for brexanolone in PPD in the United States. We expect to submit the NDA in the first half of 2018. We have also received PRIority MEdicines, or PRIME, designation from the European Medicines Agency, or EMA, for brexanolone in the treatment of PPD in the EU. We anticipate that planned discussions with the EMA will better inform timing of our planned marketing authorization application, or MAA, submission, any additional work required, the potential for conditional or full marketing approval and potential post-marketing clinical development obligations if our application is approved.

PPD is a distinct and readily identified major depressive disorder that is a common biological complication of childbirth, affecting a subset of women typically commencing in the third trimester of pregnancy or in the months after giving birth. PPD often leads to devastating consequences for a woman and for her family, which may include:

- significant functional impairment;
- depressed mood and/or loss of interest in the newborn, and;
- associated symptoms of depression such as loss of appetite, difficulty sleeping, motor challenges, lack of concentration, loss of energy and poor self-esteem.

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Suicide is the leading cause of maternal death following childbirth. It is estimated that PPD affects approximately 10 to 20 percent of women giving birth globally. In the United States, 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 greater than 400,000 or more women in the United States each year may experience PPD. There are no pharmacological therapies specifically approved for PPD.

The Hummingbird Phase 3 program included two Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trials designed to evaluate the safety and effectiveness of brexanolone in women with moderate and severe PPD. 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 in both trials at all doses, brexanolone achieved the primary endpoint, a statistically significant mean reduction from baseline in the Hamilton Rating Scale for Depression, or HAM-D, total score at 60 hours compared to placebo (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). Patients treated with brexanolone demonstrated mean reductions from baseline in HAM-D total scores of 14 to 20 points at 60 hours maintained to 30 days in both trials, demonstrating duration of therapeutic effect. Brexanolone was generally well tolerated and showed a similar safety profile as seen in earlier studies.

In Study 202B, 138 women with severe PPD as measured by a HAM-D 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 HAM-D total score of 17.7 points from baseline compared with a 14.0 point mean reduction in HAM-D total score associated with placebo (p=0.0252). Brexanolone 60 µg/kg/hour treatment was associated with a statistically significant mean reduction in HAM-D total score of 19.9 points from baseline compared with a 14.0 point mean reduction in HAM-D total score associated with placebo (p=0.0013). Reduction in HAM-D total score of brexanolone versus placebo were first observed at 48 hours (p=0.011 for 60 µg/kg/h dose and p=0.0511 for 90 µg/kg/h dose), and the effect at 60 hours was maintained at the 30-day follow-up with statistical significance for both brexanolone dose groups at 30 days. Improvement in the Clinical Global Impression Improvement scale (CGI-I) 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 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 HAM-D total score of 14.2 points from baseline at 60 hours (p=0.016) compared with a 12.0 point mean reduction in HAM-D 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. Improvement in the Clinical Global Impression Improvement scale (CGI-I) at 60 hours was consistent with the primary endpoint (p=0.0005).

Brexanolone was generally well tolerated in both trials with similar rates of adverse events across all treatment groups. One patient experienced two serious adverse events in each Phase 3 PPD trial; neither required hospitalization and both serious adverse events in one subject in Study 202B were deemed by the investigator not to be study-drug related.

We have received Breakthrough Therapy designation from the FDA for brexanolone as a potential treatment for PPD. Based on input we received from the FDA during a Breakthrough Therapy meeting,

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we believe the results of the Phase 3 clinical program, together with the results of prior clinical trials and nonclinical studies of brexanolone in PPD, will be sufficient to support the submission of an NDA to the FDA seeking approval for brexanolone in PPD in the United States. We expect to submit the NDA in the first half of 2018. We anticipate that planned discussions with the EMA will better inform timing of our planned MAA submission, any additional work required, the potential for conditional or full marketing approval and potential post-marketing clinical development obligations if our application is approved. If approved as a treatment for PPD, brexanolone would be administered intravenously for 60 hours.

We are in the process of preparing for a potential commercial launch of brexanolone IV in PPD in the United States in the first half of 2019. Our ability to launch brexanolone IV in the United States is dependent on the successful filing of an NDA with the FDA, and obtaining FDA approval, in each case on our expected timelines. As part of our ongoing launch readiness efforts in the United States, we are continuing to build the teams, infrastructure, systems, processes, policies, relationships and materials necessary for launch of brexanolone IV in the United States in PPD, including in sales; marketing; market access; patient support; medical affairs; distribution; quality; compliance; and other key functional areas. If the NDA for brexanolone IV is approved by the FDA, we anticipate deploying a field sales force team of approximately 50 key account managers calling on hospitals and approximately 200 specialty representatives calling on healthcare professionals who treat in an outpatient setting. As we continue to build our market access capabilities, we are engaging in permitted discussions with payors as we plan for a potential launch. We are also focused on enabling appropriate sites of care for administering brexanolone IV, including the potential for home infusion. If approved as a treatment for PPD, brexanolone IV would be administered intravenously for 60 hours. In addition to our efforts in the United States, we are refining our strategy and market assessments with respect to a potential launch in the E.U. We also plan to continue to evaluate market opportunities for brexanolone IV in PPD in other global markets.

In the third quarter of 2017, we announced results of a Phase 3 clinical trial of brexanolone in super-refractory status epilepticus, or SRSE. The trial did not meet its primary endpoint of comparing success in weaning of third-line agents and resolution of status epilepticus in SRSE patients treated with brexanolone versus placebo when added to standard-of-care. We are continuing to analyze the Phase 3 data, but do not currently plan to pursue brexanolone as a treatment for SRSE.

Our most advanced next-generation product candidate is SAGE-217, 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 currently developing SAGE-217 as a potential treatment for several mood disorders: major depressive disorder, or MDD, bipolar depression, and PPD, and also in Parkinson s disease and insomnia.

In December 2017, we announced positive top-line data from a double-blind, placebo-controlled Phase 2 clinical trial of SAGE-217 in 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 HAM-D 17-Item 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 HAM-D 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 the results at week 6 were not statistically significant. At Day 15, 64 percent of patients who received SAGE-217 achieved remission, defined as a score of 7 or less on the HAM-D 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 or severe adverse events. The overall number of reports of adverse events were similar between drug (53%) and placebo (46%). A low rate of discontinuations due to adverse events was reported. Based on these results, we expect to

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initiate additional clinical trials of SAGE-217 in MDD and to commence initial clinical development of SAGE-217 in bipolar depression in 2018. In February 2018, we received Breakthrough Therapy designation from the FDA for SAGE-217 as a potential treatment for MDD.

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. We believe the results of this Phase 1/2 trial will provide guidance on the potential clinical development of SAGE-217 in sleep disorders, which we expect to commence in 2018.

In November 2017, we reported results from an open-label exploratory Phase 2 clinical trial evaluating SAGE-217 as an adjunctive treatment to anti-Parkinsonian agents in 14 patients with tremor-predominant Parkinson s disease. The clinical trial of SAGE-217 met its primary efficacy endpoint of improving tremor symptoms, as assessed by the Movement Disorder Society Unified Parkinson s Disease Rating Scale, or MDS-UPDRS, Part II/III tremor score, by a mean change of 7.7 points (40.0%) by Day 8 from a mean baseline of 19.1 points. Additional secondary efficacy endpoints were consistent with the primary efficacy endpoint. SAGE-217 improved overall Parkinson s disease motor symptoms, as assessed by the MDS-UPDRS Part III motor score, by a mean change of 18.6 points (36.3%) by Day 8 from a mean baseline score of 52.4 points. SAGE-217 also improved symptoms of sleep dysfunction in five patients with clear sleep dysfunction at baseline, as assessed by the Parkinson s Disease Sleep Scale (PDSS-2) score, by a mean change of 12.2 points (41.2%) by Day 8 from a mean baseline score of 29.8 points. The most common adverse events observed in the trial were dizziness, sedation and somnolence, each occurring in two patients. We believe the results of this open-label Phase 2 trial will provide guidance on methodology, dosing, and design for a planned placebo-controlled Phase 2 clinical trial of SAGE-217 in Parkinson s disease patients with residual tremor, which we expect to commence in 2018.

In late 2017, we completed Part C of an exploratory open-label Phase 2 clinical trial of SAGE-217 in 18 patients with essential tremor studying higher doses than doses studied in Part A and B of the open-label trial and evaluating extended dosing. In Part C, SAGE-217 improved tremor symptoms, as assessed by the Kinesia Upper Limb Combined Score, by 16% on Day 15 following two weeks of dosing, although the improvement was not statistically significant. Administration of SAGE-217 in Part C was generally well-tolerated. There were no serious adverse events reported in Part C. Reductions in kinetic tremor measures of up to 21% at 40mg observed in Part C suggest twice-daily dosing may be preferable for this indication. In November 2017, we announced results of Part A of the Phase 2 trial, based on data generated prior to discontinuation of enrollment. Part A was an open-label trial with morning dosing of SAGE-217 for seven days, enrolling 16 patients diagnosed with essential tremor, defined as visible and persistent bilateral postural tremor and kinetic tremor, involving hands and forearms, with a duration greater than five years prior to screening. In Part A, SAGE-217 improved tremor symptoms, as assessed by the TETRAS upper limb combined kinetic score, by at least 30% on Day 7 in 8/12 patients (67%) who received SAGE-217 oral capsule in the trial for the entire seven days, which was the pre-established success criteria for moving to the next part of the trial. Administration of SAGE-217 in the morning was generally well-tolerated. The most common adverse events were somnolence, dizziness, and sedation. There were no serious adverse events reported in the 14 patients receiving SAGE-217 oral capsule. There was one serious adverse event reported as

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confusion in one of the two patients who received SAGE-217 oral solution prior to transition to the capsule form of administration. In conjunction with changes in the Phase 2 trial design and commencement of Part C, Part B of the trial was discontinued, and there was an insufficient number of patients enrolled prior to enrollment to generate meaningful data. Based on the results we have seen with respect to SAGE-217 in this indication, we have decided to transition development of our $GABA_A$ program for essential tremor from SAGE-217 to SAGE-324, which we believe has a profile suited for twice-daily dosing.

We are also currently conducting a blinded, placebo-controlled Phase 2 clinical trial of SAGE-217 in PPD. In February 2018, we decided to increase the number of patients in the trial even further than the prior increase at the end of 2017 from approximately 66 patients to approximately 140 patients in order to increase the power of the trial from 80% to 90%. As a result of that change we now expect to report top-line results from this trial in the fourth quarter of 2018.

The following table summarizes the status of our development programs as of the date of this prospectus supplement.

We have a portfolio of other novel compounds that target $GABA_A$ receptors, including SAGE-324 and SAGE-689, which are at earlier stages of development with a focus on both acute and chronic CNS disorders. SAGE-324 is currently in IND-enabling studies, and is intended to be developed with a focus on epileptiform disorders and essential tremor. SAGE-689 is at the preclinical stage of development as we evaluate possible alternative formulations. We also have earlier stage GABA compounds and programs such as SAGE-105 and our ST-320 and ST-500 programs.

Our second area of focus is the development of novel compounds that target the NMDA receptor. The first product candidate selected for development from this program is SAGE-718, an oxysterol-based positive allosteric modulator of the NMDA receptor. Our initial areas of focus for development of SAGE-718 are expected to be indications involving NMDA receptor hypofunction. Examples of these potential areas for future evaluation include certain types, aspects or subpopulations of a number of diseases such as depression, Alzheimer s disease, attention deficit hyperactivity disorder, schizophrenia, Huntington s disease, and neuropathic pain. We commenced the Phase 1 clinical program for SAGE-718 in the second quarter of 2017. In November 2017, we reported results from a Phase 1 single ascending dose trial of SAGE-718 in healthy volunteers. The primary objectives of the trial were to assess the

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safety, tolerability, and pharmacokinetics of SAGE-718. In the single ascending dose trial, SAGE-718 was administered as an oral solution in four double-blind placebo-controlled cohorts (randomized 6:2) enrolling a total of 32 healthy volunteers. SAGE-718 was well-tolerated in the trial with no serious adverse events reported. The pharmacokinetics of SAGE-718 observed in the trial were highly predictable with low variability. Based on these results, we plan to initiate a Phase 1 multiple ascending dose trial. We are also investigating the effects of SAGE-718 on pharmacodynamic biomarkers. We have also initiated IND-enabling studies of SAGE-904, another positive allosteric modulator of the NMDA receptor.

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

We have not generated any revenue to date. We have incurred net losses in each year since our inception, and we have an accumulated deficit of $521.0 million as of September 30, 2017. Our net losses were $200.7 million for the nine months ended September 30, 2017 and $159.0 million for the year ended December 31, 2016. These losses have resulted principally from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to incur significant expenses and increasing operating losses for the foreseeable future.

We issued 4,058,822 shares of common stock in an underwritten public offering, completed on November 17, 2017, or the November 2017 Offering. Including such issuance, we had 42,002,934 shares of common stock outstanding as of December 31, 2017.

Our strategy

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

- Seek regulatory approval of our proprietary IV formulation of brexanolone in PPD in the United States and the E.U., and potentially in other markets where it may make business and strategic sense for us to proceed;

- Build the commercial capability to bring our IV formulation of brexanolone to the market for the treatment of PPD, and commercialize the product in the United States, if and when approved, and to be prepared to market our other central nervous system product candidates, if and when approved for their target indications;

- Advance development of SAGE-217, in parallel with brexanolone in one or more of MDD, bipolar depression, PPD, Parkinson s disease, and insomnia;

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Advance SAGE-324 in IND-enabling studies with a potential future development focus on epileptiform disorders and essential tremor;

Advance SAGE-718, our novel allosteric modulator for NMDA, through completion of ongoing Phase 1 clinical trials, and, if successful, move into later-stage clinical trials;

Continue our research and development efforts to evaluate the potential for our existing product candidates in the treatment of additional indications, and the identification of new drug candidates in the treatment of CNS disorders;

Enhance the probability of success in treating CNS disorders by developing unique assets with differentiated features, and focus our internal development activities on CNS indications where we can make well-informed, rapid go/no-go decisions; and

Grow our pipeline more broadly utilizing the strengths of our proprietary chemistry platform and scientific know-how, to lessen our long-term reliance on a single franchise and to facilitate long-term growth.

Company information

We were incorporated in Delaware in April 2010. Our mailing address and executive offices are located at 215 First Street, Cambridge, Massachusetts, 02142, and our telephone number is (617) 299-8380. We maintain an Internet website at the following address: www.sagerx.com. The information on, or that can be accessed through, our website does not constitute part of this prospectus supplement or the accompanying prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock. Our common stock trades on The Nasdaq Global Market under the symbol SAGE .

Risks related to our business

We are a clinical-stage biotechnology company, and our business and ability to execute our business strategy are subject to a number of risks of which you should be aware before you decide to buy our common stock. In particular, you should consider the following risks, which are discussed more fully in the section entitled Risk Factors in this prospectus supplement and in our Annual Report on Form 10-K for the fiscal year ended December 31, 2016 and in our Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2017, which are incorporated herein by reference:

We depend heavily on the success of our current product candidates, of which brexanolone has completed Phase 3 clinical development for PPD; SAGE 217 has only completed one placebo-controlled trial in MDD to date. We cannot be certain that we will be able to submit an NDA with the FDA and MAA with the EMA for our proprietary formulation of brexanolone in PPD as planned or within the time-frames we expect, and we cannot be certain we will receive approval. We cannot be certain we will be able to complete ongoing and planned clinical trials and nonclinical studies of our other product candidates, or announce results, on the time-lines we expect. We cannot be certain that we will be able to advance our product candidates into additional trials, or to successfully develop, or obtain regulatory approval for, or successfully commercialize, any of our product candidates;

Clinical trial results are subject to interpretation and we cannot be certain that the results of our completed Phase 3 clinical trials of brexanolone in PPD are sufficient to support acceptance for filing or approval of an NDA or MAA in PPD. Regulatory authorities may, despite prior advice on development, decide that the clinical and nonclinical data from our brexanolone development program in PPD are not sufficient to support filing for regulatory approval or the acceptance of the NDA or MAA for review or do not support the grant of regulatory approval,

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and may require additional trials, analyses or data. If our NDA or MAA for brexanolone as a potential treatment for PPD is not filed, accepted for review and approved, it could materially adversely affect our business and the value of our common stock. We cannot be certain that issues will not arise during inspections by regulatory authorities of our facilities, data and systems or those of our contract research organizations, contract manufacturers or clinical sites that could delay or prevent us from gaining approval of brexanolone IV;

We cannot be certain that the results of clinical trials or nonclinical studies of any of our other product candidates will be positive or support further development. Positive results from earlier nonclinical studies and clinical trials of our product candidates are not necessarily predictive of the results of later nonclinical studies and clinical trials with the same or different compounds. If we cannot replicate the positive results from our earlier nonclinical studies and clinical trials of our product candidates in our later nonclinical studies and clinical trials or if other negative data is generated, we may be unable to successfully develop, obtain regulatory approval for and commercialize our product candidates;

The number of patients with PPD, MDD, bipolar depression, Parkinson s disease, and the other diseases and disorders for which we are developing product candidates has not been established with precision. 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, we have applied assumptions and assessments with respect to available information that may not prove to be correct. In each case, there is a range of estimates in the published literature which include estimates within the range that are lower than our estimates. For example, our estimates of the prevalence of PPD are higher than estimates reported in some of the published literature or results obtained from certain studies analyzing limited claims databases. We believe this difference is due to variations in methodologies and a possible 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, Parkinson s disease, bipolar depression or any other indication in which we elect to pursue development of our product candidates may, however, be significantly lower than our estimates. In addition, our products, if approved, may be approved for use or used in only a subset of the patients with these diseases or disorders. If the actual number of patients with these diseases or disorders or any other diseases or disorders we elect to pursue with our product candidates, or the subset that is appropriate for use of our product candidates, is smaller than we anticipate, we may encounter difficulties in enrolling patients in our clinical trials, thereby delaying completion of our clinical trials or delaying or preventing development of our product candidates, and even if such product candidates are approved, our revenue and ability to achieve profitability may be materially adversely affected;

The identification of serious adverse events or other undesirable side effects during the use of brexanolone IV, SAGE-217, SAGE-718 or any of our other product candidates in ongoing or planned clinical trials, emergency-use cases, investigator sponsored trials, expanded access programs, or nonclinical studies may adversely affect our development of such product candidates or our ability to obtain regulatory approval;

The reported results of our Phase 3 clinical trials of brexanolone in PPD and Phase 2 clinical trial of SAGE-217 in MDD and other indications consist of only top-line data from the study. Top-line data are based on a preliminary analysis of currently available efficacy and safety data, and therefore these currently reported results are subject to change following a comprehensive review of the more extensive data we expect to receive. The top-line data are based on important assumptions, estimations, calculations and information currently available to us, and we have not received or had an opportunity to evaluate all of the data from these

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trials. As a result, we may have additional or different conclusions or conclusions that may qualify the top-line results, once the complete data have been received and fully evaluated. If the full data set or conclusions from the full data set differ from the top line data reported, our ability to obtain approval for, and commercialize, brexanolone IV for PPD, or our view as to the opportunity for SAGE-217 for MDD and other indications, may be harmed, which could materially adversely affect our business, financial condition, results of operations and prospects and the value of our common stock;

We cannot be certain as to what the FDA or other regulatory authorities will require in future clinical trials of SAGE-217 in MDD. For example, the FDA may require different endpoints than those studied in our earlier trials. Even if the endpoints are the same, the earlier studies of SAGE-217 in MDD may not be predictive of the results obtained in future studies;

We may face challenges in identifying, recruiting and enrolling patients to participate in clinical trials, including and due to: the small size of a patient population; the acute nature of a disease; 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 United States; 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, and such challenges may delay enrollment of patients in existing or future clinical trials of our other product candidates. Failures or delays in completion of our ongoing and planned clinical trials of our product candidates could cause us not to meet our expected timelines or result in increased costs to us, and could delay, prevent or limit our ability to gain regulatory approval of any product candidate and generate revenue and continue our business;

A Fast Track designation or Breakthrough Therapy designation by the FDA and PRIME designation by the EMA may not actually lead to a faster development or regulatory review or approval process. Changes in regulatory requirements, regulatory authority guidance or unanticipated events during our nonclinical studies and clinical trials of our product candidates may occur, which may result in changes in requirements with respect to nonclinical studies and clinical trial protocols or result in the need for additional nonclinical studies and clinical trial requirements, which could result in increased costs to us and could delay our development timeline. The drug development process can take many years, and may include post-marketing studies and surveillance, which will require the expenditure of substantial resources. For example, of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized;

Even if we receive marketing approval for our product candidates, regulatory or other governmental authorities may still impose significant restrictions on our products, including restrictions on indicated uses or marketing, or may impose ongoing requirements for potentially costly post-approval studies. For example, if we are successful in our efforts to obtain approval of brexanolone IV and other product candidates, we expect that, prior to product launch, the U.S. Drug Enforcement Agency, or DEA, will need to determine the controlled substance schedule of brexanolone IV and possibly such other product candidates, taking into account the recommendation of the FDA. The process may delay our ability to market any such product if it is approved. Any of these factors, many of which are beyond our control, could jeopardize or delay our ability to obtain regulatory approval for and successfully market our product candidates. Any such setback would have a material adverse effect on our business and prospects. Even if we receive marketing approval in the United States, we may never seek or receive regulatory approval outside the United States;